**REMARKS**

The Office Action of January 27, 2000 presents the examination of claims 6-9, 12 and 13. Claims 6-9, 12, and 13 are amended. No new matter is inserted into the application.

***Claim Objections***

The Examiner objects to claim 6 for being dependent from non-elected claims. Applicants amend claim 6 into independent form. Thus, the instant objection is overcome.

***Rejection under 35 U.S.C. § 112, second paragraph***

Claims 6-9 and 12-13 are rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

A. The Examiner asserts that the phrase "capable of yielding" in claims 6-9 and 12-13 is not clear. In response to the Examiner's remarks, Applicants amend the phrase to "yields." Thus, the instant rejection is overcome.

B. The Examiner asserts that the phrase "through intracellular decomposition" in claims 6-9 and 12-13 is not clear. In response to the Examiner's remarks, Applicants amend the phase to "through intracellular processing." The term "processing" is

widely used in the art and therefore comports with the statute. As evidence thereof, Applicants submit the following journal article as Exhibit 1 (attached hereto): *Nature Medicine*, 1:1140 (1995). See, for example, page 1140, left column, second full paragraph, line 12. It is well known in the art that peptides are processed and presented on MHC molecules. As recited in MPEP 2173.02 (page 2100-146), "Definiteness of claim language must be analyzed not in a vacuum, but in light of … the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art." For these reasons, one of skill in the art can clearly determine the scope of the claims. As such, the instant rejection is overcome.

C. The Examiner asserts that the phrase "functionally equivalent properties" in claims 7-8 and 12-13 is unclear. In response to the Examiner's remarks, Applicants delete said phrase. Thus, the instant rejection is overcome.

D. The Examiner asserts that the phrases "derivative" and "derivate" in claims 7-8 and 12-13 is indefinite. In response to the Examiner's remarks, Applicants delete these phrases. Thus, the instant rejection is overcome.

E. The Examiner rejects the phrase "a tumor antigen produced by the expression." In response to the Examiner's remarks, Applicants delete said phrase. Thus, the instant rejection is

overcome.

F. The Examiner rejects the phrase "stringent conditions" in claims 6-9 and 12-13. In response to the Examiner's remarks, Applicants amend the phrase to "stringent conditions comprising 6xSSC, 50% formamide, and 0.5% SDS and a temperature of 42$^0$C" as disclosed on page 11, lines 17-19 of the instant specification. Thus, the instant rejection is overcome.

G. The Examiner rejects claims 12-13 for the use of the term "medicine." In response to the Examiner's remarks, Applicants amend the term to "composition," as suggested by the Examiner. Thus, the instant rejection is overcome.

Applicants respectfully submit that the above amendments render the instant claims in full compliance with 35 U.S.C. § 112, second paragraph. Thus, Applicants respectfully request that the instant rejection applied to the claims is withdrawn.

***Issues under 35 U.S.C. § 112, First Paragraph***

The Examiner rejects claims 6-9 and 12-13 under 35 U.S.C. § 112, first paragraph, for allegedly being not enabled by the instant specification. Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

First, the Examiner asserts that the specification does not provide enablement for "any variant protein of SEQ ID NO:2 which contains any unspecified number of substitutions, deletions, additions, or derivatives." In response to the Examiner's remarks, the claims are amended so that "any variant protein of SEQ ID NO:2" is not claimed. Thus, the instant rejection is overcome.

Second, the Examiner asserts that the specification does not provide enablement for any "variant DNA which hybridizes to the DNA of SEQ ID NO:1 under any stringent conditions." In response to the Examiner's remarks, the claims are amended so that "any stringent conditions" is not claimed. Specifically, the claims now recite the stringent hybridization conditions of 6xSSC, 50% formamide, and 0.5% SDS and a temperature of 42$^0$C (as disclosed on page 11, lines 17-19 of the instant specification). It is noted that these hybridization conditions are substantially the same as those recited in Example 9 of the USPTO Revised Interim Written Description Guidelines Training Materials. Further, one of the most famous manuals used in the art, *Molecular Cloning, a Laboratory Manual* (attached hereto as Exhibit 2), states that standard hybridization conditions routinely used in the art is 68$^0$C in aqueous solution or 42$^0$C in 50% formamide (see page 324, line 6). Finally, the instant specification specifically provides the hybridization conditions in Examples 2 and 3. Thus, the instant rejection is overcome.

Third, the Examiner rejects claims 12 and 13 for being "broadly drawn to a medicine…." In response to the Examiner's remarks, Applicants amend the term to "composition," as suggested by the Examiner. Thus, the instant rejection is overcome.

For all of the above reasons, Applicants respectfully submit that all of the instant claims comply with 35 U.S.C. § 112, first paragraph, and respectfully request that the instant rejection be withdrawn.

***Rejection Under 35 U.S.C. § 102***

The Examiner rejects claims 6-9 and 12-13 under 35 U.S.C. § 102(b) for allegedly being anticipated by Nakao et al. (*Cancer Res.* 55:4248-4252). Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

Nakao et al. discloses a peptide antigen expressed on SCC from KE-4 tumor cells. The Examiner asserts that the peptide antigens disclosed by Nakao et al. are the same peptide antigens of the present invention, absent evidence to the contrary.

In order to overcome this rejection, Applicants submit herewith a Declaration executed by Dr. Itoh (first named Inventor) demonstrating that the claimed peptide antigens are distinct from those disclosed by Nakao et al. A signed Declaration will follow. First, however, Applicants note that there are plural tumor antigen

proteins expressed on KE-4 and recognized by KE-4CTL, and, in addition, the active fraction No. 23 of Fig. 3 on page 4251 of Nakao et al. does not necessarily indicate that the fraction contains *any* isolated tumor antigen peptide or protein, much less the tumor antigen protein/peptide of the present invention. Thus, the possibility that Nakao et al. even discloses a single isolated tumor antigen peptide has not been established.

Nevertheless, the Declaration attached hereto shows that the inventive tumor antigen protein/peptide was only capable of isolation and identification through the technique of expression cloning (see 5.1.3.). It is known in the art that HPLC, when conducted under the conditions recited in Nakao et al., results in peaks containing plural peptides. In other words, the active peak (No. 23) corresponds to a mixture of peptides of unknown structure. Thus, such a disclosure of multiple peptides of unknown structure clearly does not anticipate an isolated tumor antigen protein or peptide of known structure (see 5.2.4.).

For the above reasons, Applicants respectfully submit that Nakao et al. fails to anticipate the present invention. Withdrawal of the instant rejection is therefore requested.

The Examiner rejects claims 6-8 and 12-13 under 35 U.S.C. § 102(e) for allegedly being anticipated by Tsui '667 (U.S.P. 5,776,667). Applicants respectfully traverse. Reconsideration of

the claims and withdrawal of the instant rejection are respectfully requested.

The Examiner writes, "Because the claims recite all or part of the amino acid sequence of 785-793, the art of Tsui et al. reads on the claims." In response to the Examiner's remarks, Applicants amend claims 7 and 8 to delete the phrase "all or part." Thus, the instant claims do not read on Tsui '667, and the instant rejection is overcome.

The Examiner rejects claims 6-9 and 12-13 under 35 U.S.C. § 102(e) for allegedly being anticipated by Boon et al. (*J. Exp. Med.* 183:725-729, 1996). Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

The Examiner asserts, "The protein of Boon et al. is a variant of the claimed protein and peptides and it would be inherent that the Boon et al. protein would contain peptides that would also bind to MHC claim I antigen and be recognized by T cells." Applicants respectfully disagree. According to the journal article by Nicolina Renkvist, et al., *Cancer Immunol. Immunother.* (2001) 50:3-15 (attached hereto as Exhibit 3) that provides the list and classification of tumor antigen peptides identified so far, the peptide of the present invention (named "SART-1") and that of Boon et al. (named "MAGE") are divided into different groups. See page

5, Table 1 and page 7, Table 3 of Renkvist et al. These Tables show that these peptides are utterly different in terms of classification, origin, distribution of expression, and structure. Accordingly, Boon et al. fails to anticipate the present invention as claimed. Withdrawal of the rejection is therefore respectfully requested.

Overall, the present invention possesses significant patentable features that the cited prior art references do not possess. Furthermore, Applicants submit that amendments to the instant claims render them fully in compliance with 35 U.S.C. § 112, first and second paragraphs. All of the present claims define patentable subject matter such that this application should be placed into condition for allowance. Early and favorable action on the merits of the present application is thereby requested.

If there are any minor matters precluding allowance of the present application which may be resolved by a telephone discussion, the Examiner is respectfully requested to contact Kristi L. Rupert, Ph.D. (Reg. No. 45,702) at (703) 205-8000.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant(s) respectfully petition(s) for a two (2) month extension of time for filing a reply in connection with the present application, and the required fee of $380.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By #32,868

For Gerald M. Murphy, Jr., #28,977

P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

GMM/KLR/csp/jms

Attachments: Exhibit 1: STROMINGER, J.L. Nature Med.,vol.1 (1995)
Exhibit 2: MANIATIS, T. et al. (1992)
Exhibit 3: RENKVIST, Nicolina et al. (2001)
Declaration Under 37 C.F.R. § 1.132

***Version to Show Changes Made:***

Claim 6 **(Amended)**

An isolated **[**A**]** tumor antigen protein selected from the group consisting of:

(a) a protein comprising an amino acid sequence shown in SEQ ID NO:1;

(b) a protein encoded by a DNA comprising a nucleotide sequence shown in SEQ ID NO:2; and

(c) a protein encoded by a DNA which hybridizes to a compliment of the DNA of SEQ ID NO:2 under stringent hybridization conditions comprising 6xSSC, 50% formamide, and 0.5% SDS and a temperature of 42$^{0}$C, wherein said protein yields, through intracellular processing, peptide fragment(s) which binds to major histocompatibility complex (MHC) class I antigen and is recognized by cytotoxic T lymphocytes (CTLs) in such binding state **[**produced by expression of DNA of claim 1 or 2**]**.

Claim 7 **(Amended)**

An isolated **[**A**]** tumor antigen peptide consisting of **[**comprising**]** part of the protein of claim 6, which binds **[**can bind**]** to MHC class I antigen to be recognized by CTLs **[**T cells, or a derivative thereof having functionally equivalent properties**]**.

Claim 8 **(Twice Amended)**

An isolated [A] tumor antigen peptide of claim 7 which comprises [all or part of] the amino acid sequence of positions 749-757, 736-744, 785-793, or 690-698 in the amino acid sequence of SEQ ID NO:1 [SEQ ID NO:2, or a derivative thereof having functionally equivalent properties].

Claim 9 **(Amended)**

A composition [medicine] comprising, as an active ingredient, the tumor antigen protein of claim 6 [the tumor antigen peptide R derivative thereof defined in claim 7 or 8].

Claim 12 **(Amended)**

A composition [medicine] comprising, as an active ingredient, the tumor antigen peptide of [or derivate thereof as defined in] claim 7.

Claim 13 **(Amended)**

A composition [medicine] comprising, as an active ingredient, the tumor antigen peptide of [or derivate thereof as defined in] claim 8.

Exhibit 1



# Peptide vaccination against cancer?

**Micrometastases in a murine lung carcinoma model have regressed or been prevented (pages 1179–1183).**

JACK L. STROMINGER

The development of our knowledge of antigen processing and presentation, and of techniques for the isolation of MHC molecules and analysis of their bound peptides, presents the opportunity to solve problems of great medical importance. These include efforts to blockade, anergize or delete T cells that mediate autoimmune diseases, as well as efforts to enhance immunity to infectious agents and tumours. A striking application to the prevention of metastatic disease in the murine Lewis lung carcinoma model is described in this issue of *Nature Medicine*[1].

The possibility of immunotherapy for human tumours is offered by the facts that some tumours (particularly melanoma and renal carcinoma) rarely undergo spontaneous remission and that low-level immune responses against some other tumours have been detected. These and other facts have led to much research aimed at identifying both tumour-specific antigens that can stimulate immune responses and ~~the peptides from the processed antigens that are presented to the immune system by MHC molecules~~. In many cases, these tumour antigens are normal self-proteins with a limited cell/tissue distribution, but they may also occur in the tumour in a mutated form or be derived from virus-associated cancers. In these latter cases they would behave immunologically as foreign proteins/peptides, although self peptides can also induce immune responses.

Several genes encoding tumour antigens that may give rise to low-level immune responses in experimental animals and man have been described[2–4]. In addition, several peptide epitopes, presented by class I MHC molecules to T cells derived from tumour hosts, have been identified. These include, notably, mutant peptide(s) derived from the gap junction protein connexin-37 found in the murine Lewis lung carcinoma[5] and peptides from several different human melanoma proteins[6–9]. In addition, nine peptides from the oncogenic E6 and E7 proteins of human papilloma virus associated with cervical carcinoma that bind to HLA-A2 were identified. Four of these induced a vigorous cytoxic T-lymphocyte (CTL) response in HLA-A2 transgenic mice, and human CTL generated with these same peptides could lyse an HLA-A2 cervical carcinoma cell line[10]. Many other class I restricted peptides have also been under study[2–4]. However, in addition to class I-MHC-restricted CD8$^+$ T-cells, class II MHC-restricted CD4$^+$ T-cells can also mediate a cytolytic response[11], a fact of particular importance in the tissue destruction in some class II-associated autoimmune diseases. Notably, therefore, a peptide of 25 residues presented by a murine class II MHC protein has been identified that is associated with an immune response against a murine tumour[12].

Can such peptides be utilized in the therapy of tumours? Therapeutic goals might include prophylaxis against some tumours (vaccination), prevention of metastatic spread after surgical removal of tumours or resolution of the tumour mass itself. Several reports addressing these questions have appeared and many more studies must be in progress. For example, vaccination has protected against a tumour formed using a transformed mouse cell line[13], and established tumours in the mouse have also been eradicated using CTL raised against the same peptide[14]. Vaccination trials in humans have been initiated. Remarkably, in the present study[1], metastatic spread from a primary tumour mass that was allowed to develop for 30 days before surgical exicision and vaccination has been prevented. If these animal studies can be extended to examples of human tumours, than a window may have opened on a rational approach to the immunotherapy of at least a few human cancers.

The mode of administration of peptides is of critical importance in such trials, because soluble peptide is thought to induce tolerance (and thus may be important in the treatment of autoimmune diseases). In the present animal studies[1] which were designed to enhance immunity, peptide was administrated in incomplete Freund's adjuvant, but in human trials various other techniques may be employed. For example, peptide pulsed onto autologous antigen presenting (dendritic) cells, encapsulated in liposomes or modified as lipopeptides have all been explored. DNA vaccination simultaneous use of cytokines that may enhance immunogenicity and the linkage of CTL epitopes to helper T-cell epitopes are among other factors that must be considered. Finally, despite all efforts, tumour escape variants may constitute a major problem. Generalized loss of expression of MHC antigens or allele-specific loss are thought to represent major problems in the immune surveillance of tumours. The road ahead is unpaved and full of potholes, but the journey could be rewarding.


1. Mandelboim, O. *et al.* Regression of established murine carcinoma metastases following vaccination with tumor associated antigen peptides. *Nature Med.* 1, 1179–1183 (1995).
2. Boon, T., Certottini, J., van den Eynde, B., van der Bruggen, P. & Van Pel, A. Tumor antigens recognized by T lymphocytes. *Annu. Rev. Immun.* 12, 337–365 (1994).
3. Nanda, N. & Sercarz, E. Induction of anti-self-immunity to cure cancer. *Cell* 82, 13–17 (1995).
4. Moller, G. Tumor immunology. *Immunol. Rev.* 145, 5–250 (1995).
5. Mandelboim, O. *et al.* CTL induction by a tumour associated antigen octapeptide derived from a murine lung carcinoma. *Nature* 369, 67–71 (1994).
6. Cox, A. *et al.* Identification of a peptide recognized by five melanoma-specific human cytotoxic T cell lines. *Science* 264, 716–719 (1994).
7. Castelli, C. *et al.* Mass spectrometric identification of a naturally processed melanoma peptide recognized by CD8$^+$ cytotoxic T lymphcytes. *J. exp. Med.* 181, 363–368 (1995).
8. Van den Eynde, B. *et al.* A new family of genes coding for an antigen recognized by autologus cytolytic T lymphocytes on a human melanoma. *J. exp. Med.* 182, 689–698 (1995).
9. Wolfel, T. *et al.* A p16-INK4a-insensitive CDK4 mutant targeted by cytolytic T lymphocytes in a human melanoma. *Science* 269, 1281–1284 (1995).
10. Ressing, M. *et al.* Human CTL epitopes encoded by human papillomavirus type 16 E6 and E7 identified through in vivo and in vitro immunogenicity studies of HLA-A*0201-binding peptides. *J. Immun.* 154, 5934–5943 (1995).
11. Krensky, A., Reiss, C., Mier, J., Strominger, J. Burakoff, S. Long-term human cytolytic T-cell lines allospecific for HLA-DR6 antigen are OKT4+. *Proc. natn. Acad. Sci. U.S.A.* 79, 2365–2369 (1982).
12. Monach, P., Meredith, S., Siegel, C. & Schreiber, H. A unique tumor antigen produced by a single amino acid substitution. *Immunity* 2, 45–49 (1995).
13. Melief, C. & Kast, M. T-cell immunotherapy of tumors by adoptive transfer of cytotoxic T lymphocytes and by vaccination with minimal essential epitopes. *Immunol. Rev.* 146, 167–177 (1995).
14. Feltkamp, M. *et al.* Cytotoxic T lymphocytes raised against a subdominant epitope offered as a synthetic peptide eradicate human papillomavirus type 16-induced tumors. *Eur. J. Immunol.* 25, 2638–2642 (1995).


*Department of Molecular and Cellular Biology*
*Harvard University*
*Cambridge, Massachusetts 02138, USA*
*and the Dana Farber Cancer Institute*
*Harvard Medical School*
*Boston, Massachusetts 02115, USA*

Exhibit

Exhibit 2

# Molecular Cloning

## A LABORATORY MANUAL


T. Maniatis Harvard University

E. F. Fritsch Michigan State University

J. Sambrook Cold Spring Harbor Laboratory



Cold Spring Harbor Laboratory
1982

## HYBRIDIZATION OF DNA OR RNA IMMOBILIZED ON FILTERS TO RADIOACTIVE PROBES

There are many methods available to hybridize radioactive probes in solution to DNA or RNA immobilized on nitrocellulose filters. These methods differ in the following aspects:

- the solvent and temperature used (68°C in aqueous solution or 42°C in 50% formamide);
- the volume of solvent and the length of hybridization (large volumes for periods as long as 3 days or minimal volumes for times as short as 4 hours);
- the degree and method of agitation (continuous shaking or stationary);
- the concentration of the labeled probe and its specific activity;
- the use of compounds, such as dextran sulfate, that increase the rate of reassociation of nucleic acids;
- the stringency of washing following the hybridization.

Although the choice depends to a large extent on personal preference, we would like to offer the following guidelines.

1. Hybridization reactions in 50% formamide at 42°C are easier to set up, present less of an evaporation problem, and are less harsh on the filters than is hybridization at 68°C in an aqueous solution. The kinetics of the hybridization reaction in 80% formamide are approximately three to four times slower than in an aqueous solution (Casey and Davidson 1977). Assuming a linear relationship between the rate of hybridization and formamide concentration, the rate in 50% formamide should be two times slower than in an aqueous solution.

2. The smaller the volume of hybridization solvent, the better. The kinetics of nucleic acid reassociation are faster, and the amount of probe needed may be reduced so that the DNA on the filter acts as the driver for the reaction. All these are important parameters when detecting clones of low-abundance mRNAs. However, it is essential that sufficient liquid be present for the filters to remain at all times covered by a film of the hybridization solution.

3. Continual movement of the probe solution across the filter is unnecessary, even for a reaction driven by DNA immobilized on the filter. However, if a large number of filters are hybridized simultaneously, agitation is advisable in order to prevent the filters from adhering to each other.

4. The kinetics of the hybridization reaction are difficult to predict from theoretical considerations, partly because the exact concentration of the immobilized nucleic acid and its availability for hybridization are unknown.

When using probes made by nick translation of double-stranded DNA, the following rule of thumb is useful: Allow the hybridization to proceed for a time sufficient to enable the probe in solution to achieve 1–3× $C_o t_{1/2}$. In 10 ml of hybridization solution, 1 $\mu$g of a probe of 5-kb complexity will reach $C_o t_{1/2}$ in 2 hours. To determine the time of half-renaturation for any other probe, simply enter the appropriate values into the following equation:

$$\frac{1}{X} \times \frac{Y}{5} \times \frac{Z}{10} \times 2 = \text{number of hours to achieve } C_o t_{1/2}$$

where,

X = the weight of probe added (in $\mu$g)
Y = its complexity (for most probes, complexity is proportional to the length of the probe in kb)
Z = the volume of the reaction (in ml)

After hybridization for 3× $C_o t_{1/2}$ has been reached, the amount of the probe available for additional hybridization to the filter is negligible. For single-stranded cDNA probes, the hybridization time may be shortened since the lack of a competing DNA strand in solution favors hybridization to DNA bound to the filter.

5. In the presence of dextran sulfate, the rate of association of nucleic acids is accelerated because the nucleic acids are excluded from the volume of the solution occupied by the polymer. Their effective concentration is therefore increased. The rate of association reportedly increases 10-fold in the presence of 10% dextran sulfate (Wahl et al. 1979).
   Although dextran sulfate is useful in circumstances where the rate of hybridization is the limiting factor in detecting sequences of interest, it is unnecessary for most purposes. It is also difficult to handle because of its viscosity and sometimes can lead to high backgrounds.

6. In general, the washing conditions should be as stringent as possible; i.e., a combination of temperature and salt concentration should be chosen that is slightly (5°C) below the $T_m$ of the hybrid under study. The temperature and salt conditions can often be determined empirically in preliminary experiments where Southern blots (see pages 382ff) of genomic DNA are hybridized to the probe of interest and then washed under conditions of different stringency.

Exhibit 3

Cancer Immunol Immunother (2001) 50:3–15



REVIEW

Nicolina Renkvist · Chiara Castelli
Paul F. Robbins · Giorgio Parmiani

# A listing of human tumor antigens recognized by T cells

Received: 6 December 2000 / Accepted: 25 December 2000

**Key words** Antigens · Tumor · T cells · Epitopes

**Complete list of abbreviations of tumor antigens** *707-AP* 707 alanine proline · AFP *alpha (α)-fetoprotein* · *ART-4* adenocarcinoma antigen recognized by T cells 4 · *BAGE* B antigen · *β-catenin/m* β-catenin/mutated · *Bcr-abl* breakpoint cluster region–Abelson · *CAMEL* CTL-recognized antigen on melanoma · *CAP-1* carcino-embryonic antigen peptide-1 · *CASP-8* caspase-8 · *CDC27m* cell-division-cycle 27 mutated · *CDK4/m* cycline-dependent kinase 4 mutated · *CEA* carcino-embryonic antigen · *CT* cancer/testis (antigen) · *Cyp-B* cyclophilin B · *DAM* differentiation antigen melanoma (the epitopes of DAM-6 and DAM-10 are equivalent, but the gene sequences are different; DAM-6 is also called MAGE-B2, and DAM-10 is also called MAGE-B1) · *ELF2M* elongation factor 2 mutated · *ETV6-AML1* Ets variant gene 6/acute myeloid leukemia 1 gene ETS · *G250* glycoprotein 250 · *GAGE* G antigen · *GnT-V* N-acetylglucosaminyltransferase V · *Gp100* glycoprotein 100 kDa · *HAGE* helicose antigen · *HER-2/neu* human epidermal receptor-2/neurological · *HLA-A*0201-R170I* arginine (R) to isoleucine (I) exchange at residue 170 of the α-helix of the α2-domain in the HLA-A2 gene · *HPV-E7* human papilloma virus E7 · *HSP70-2M* heat shock protein 70-2 mutated · *HST-2* human signet ring tumor-2 · *hTERT* or *hTRT* human telomerase reverse transcriptase · *iCE* intestinal carboxyl esterase · *KIAA0205* name of the gene as it appears in databases · *LAGE* L antigen · *LDLR/FUT* low-density lipid receptor/GDP-L-fucose: β-D-galactosidase 2-α-L-fucosyltransferase · *MAGE* melanoma antigen · *MART-1/Melan-A* melanoma antigen recognized by T cells-1/melanoma antigen A · *MC1R* melanocortin 1 receptor · *Myosin/m* myosin mutated · *MUC1* mucin 1 · *MUM-1, -2, -3* melanoma ubiquitous mutated 1, 2, 3 · *NA88-A* NA cDNA clone of patient M88 · *NY-ESO-1* New York-esophagus 1 · *P15* protein 15 · *p190* minor bcr-abl protein of 190 kDa bcr-abl · *Pml/RARα* promyelocytic leukaemia/retinoic acid receptor α · *PRAME* preferentially expressed antigen of melanoma · *PSA* prostate-specific antigen · *PSM* prostate-specific membrane antigen · *RAGE* renal antigen · *RU1* or *RU2* renal ubiquitous 1 or 2 · *SAGE* sarcoma antigen · *SART-1* or *SART-3* squamous antigen rejecting tumor 1 or 3 · *TEL/AML1* translocation Ets-family leukemia/acute myeloid leukemia 1 · *TPI/m* triosephosphate isomerase mutated · *TRP-1* tyrosinase related protein 1, or gp75 · *TRP-2* tyrosinase related protein 2 · *TRP-2/INT2* TRP-2/intron 2 · *WT1* Wilms' tumor gene

**Abbreviations used** *ALL* acute lymphoblastic leukemia · *AML* acute myeloid leukemia · *APL* acute promyelocytic leukemia · *CML* chronic myelogenous leukemia · *CTL* cytotoxic T lymphocytes · *Ets* E-26 transforming specific (family of transcription factors) · *H/N* head and neck · *MHC* major histocompatibility complex · *NSCLC* non-small cell lung carcinoma · *ORF* open reading frame · *RCC* renal cell carcinoma · *SCC* squamous cell carcinoma · *TSTA* tumor-specific transplantation antigens

N. Renkvist · C. Castelli · G. Parmiani (✉)
Unit of Immunotherapy of Human Tumors,
Istituto Nazionale Tumori, Via G. Venezian 1,
20133 Milan, Italy

P. F. Robbins
Surgery Branch, National Cancer Institute, NIH,
Bethesda, Maryland, USA

## Introduction

Since the cloning of *MAGE-1* [125], the first gene reported to encode a human tumor antigen recognized by T cells, molecular identification and characterization of tumor antigens has mainly been achieved for melanoma. A major reason for this lies in the difficulty of establishing cell lines in vitro from other types of cancer, such lines being necessary to generate tumor-specific CTL

lines or clones to be used in the genetic or biochemical approach aimed at molecularly identifying new cancer antigens. More recently, however, new approaches have allowed the discovery of new antigens recognized by T cells even in tumors other than melanoma.

It is, then, important to categorize these antigens, particularly for the HLA allele restricting their recognition by T cells and for their tissue distribution. With this purpose, tumor antigens have been collected in the present work and briefly commented.

The list presented in the tables below includes all T-cell-defined epitopes encoded by tumor antigens and published by 31 July 2000. Analogs or artificially modified epitopes are excluded from the list. Only tumor antigens recognized by T cells (either cytotoxic CD8 + or helper CD4 +) are listed, given their potential importance in the control of tumor growth. Other antigens, identified by antibodies, are excluded but a large collection of them, as detected by the Serex technology, can be found in the data base of the Institute for Cancer Research (www.licr.org/SEREX.htm). It is of note that many tumor antigens (e.g. MAGE, NY-ESO-1a) are now known to be recognized by both T cells and antibodies in the same cancer patients [54].

In the tables herein, tumor antigens are listed in alphabetic order along with the epitope sequence and the HLA allele which restricts recognition by T cells. Furthermore, data on the tissue distribution of each antigen are provided, making this listing an important source for easily retrieving data concerning human tumor antigens.

The listing is meant to be a tool for scientists and students who have an interest in the field of tumor immunology and immunotherapy. The bibliography allows a rapid search for more detailed information at the single antigen or epitope level.

We do not ignore, however, the fact that by recent technologies (e.g., subtractive hybridization, representational-difference analysis, microarrays) hundreds of genes are being detected which are preferentially expressed or overexpressed in neoplastic cells as compared with normal counterparts or are expressed in metastatic but not in primary, early lesions (e.g., melanoma, breast cancer, lymphoma). By using appropriate computer algorithms [9], a number of new epitopes will be identified that can bind MHC molecules. By applying such approaches, a large array of gene products can be screened for their potential antigenic function. More cumbersome may be the selection of the most immunogenic epitopes through appropriate functional assays.

## Classification of tumor antigens

### Group 1: Class I HLA-restricted cancer/testis antigens (Table 1)

A milestone in tumor immunology was certainly the cloning of *MAGE-1* [125] and the subsequent characterization of the first T-cell-defined antigenic epitope a year later [119]. Those findings were rapidly followed by the identification of new members within this group [6, 123]. The *MAGE*, *BAGE* and *GAGE* families of genes were born. The antigens belonging to this group, now including also NY-ESO-1, were called cancer/testis (CT) antigens for their expression in histologically different human tumors and, among normal tissues, in spermatocytes/spermatogonia of testis and, occasionally, in placenta. These antigens now represent one of the main components for antitumor vaccine development. CT antigens result from reactivation of genes normally silent in adult tissues [27], but that are transcriptionally activated in some tumors [30]. Their expression in testis does not provide targets for an immune reaction because cells of testis do not express class I HLA [56]. Despite the fact that the CT genes are probably the most characterized ones, their physiological function remains largely unknown.

Considering that new genes in the group of CT antigens have been cloned (CT9 [105], CT10 [46], LAGE [72], MAGE-B5, –B6, –C2, –C3 and –D [74, 75], HAGE, SAGE [80]), but that no T-cell epitopes have been identified from them yet, the question arises as to how many more genes encoding CT antigens remain to be discovered and how many epitopes exist that could be of use in cancer immunotherapy.

### Group 2: Class I HLA-restricted differentiation antigens (Table 2)

These antigens are shared between tumors and the normal tissue from which the tumor arose; most are found in melanomas and normal melanocytes [2]. Many of these melanocyte lineage-related proteins are involved in the biosynthesis of melanin. Epitopes recognized by both CD8 + and CD4 + T cells can be derived from melanosome proteins [8, 118, 135, 136].

### Group 3: Class I HLA-restricted widely expressed antigens (Table 3)

Genes encoding widely expressed tumor antigens have been detected in many normal tissues as well as in histologically different types of tumors with no preferential expression on a certain type of cancer. It is possible that the many epitopes expressed on normal tissues are below the threshold level for T-cell recognition, while their overexpression in tumor cells can trigger an anticancer response even by breaking a previously established tolerance. These widely expressed gene products have revealed a broad spectrum of mechanisms that are involved in generating T-cell-defined epitopes through alterations in gene transcription and translation. To highlight some examples, the epitope of CEA is derived from a non-AUG-defined alternative ORF [1], while the RU2 gene creates its epitope by reverse strand transcription [124].

Table 1 Class I HLA-restricted cancer/testis antigens. All these antigens were found to be expressed by normal spermatocytes and/or spermatogonia of testis. Occasionally *MAGE-3*, *MAGE-4* and the *GAGE* genes were found to be expressed also in placenta [26, 24]. The NY-ESO-1 antigen was found to be expressed in normal ovary cells [18]

| Gene | HLA allele | Peptide epitope | Authors [ref.] | Tissue distribution among tumors[a] |
|---|---|---|---|---|
| *MAGE-A1* | A1 | EADPTGHSY | Traversari et al. 1992 [119] | Melanoma, breast carcinoma, SCLC [27, 29, 125] – sarcoma, NSCLC [27, 29] – thyroid medullary carcinoma [125] – colon carcinoma [27] – laryngeal tumors [29] |
| *MAGE-A1* | A3 | SLFRAVITK | Chaux et al. 1999a [16] | |
| *MAGE-A1* | A24 | NYKHCFPEI | Fujie et al. 1999 [37] | |
| *MAGE-A1* | A28 | EVYDGREHSA | Chaux et al. 1999a [16] | |
| *MAGE-A1, -A2, -A3, -A6* | B37 | REPVTKAEML | Tanzarella et al. 1999 [113] | Melanoma, colon and breast carcinomas, SCLC [27, 29, 125] – sarcoma, NSCLC [27, 29] – thyroid medullary carcinoma, H/N tumors, bronchial SCC [125] – laryngeal tumors [29] – leukemias [27] |
| *MAGE-A1* | B53 | DPARYEFLW | Chaux et al. 1999a [16] | Melanoma, breast carcinoma, SCLC [27, 29, 124] – sarcoma, colon carcinoma, NSCLC [27, 29] – thyroid medullary carcinoma [125] |
| *MAGE-A1* | Cw2 | SAFPTTINF | Chaux et al. 1999a [16] | |
| *MAGE-A1* | Cw3 | SAYGEPRKL | Chaux et al. 1999a [16] | |
| *MAGE-A1* | Cw16 | SAYGEPRKL | van der Bruggen et al. 1994b [127] | |
| *MAGE-A2* | A2 | KMVELVHFL | Visseren et al. 1997 [128] | Melanoma, colon and breast carcinomas, SCLC [27, 29, 125] – sarcoma, NSCLC [27, 29] – thyroid medullary carcinoma [125] – laryngeal tumors [77] – leukemias [27] |
| *MAGE-A2* | A2 | YLQLVFGIEV | Visseren et al. 1997 [128] | |
| *MAGE-A2* | A24 | EYLQLVFGI | Tahara et al. 1999 [110] | |
| *MAGE-A3* | A1 | EADPIGHLY | Gaugler et al. 1994 [40] | Melanoma, colon and breast carcinomas [27, 125] – H/N tumors [18] – bronchial SCC, thyroid medullary and bladder carcinoma, sarcomas, SCLC, NSCLC [125] – leukemias [29] |
| *MAGE-A3* | A2 | FLWGPRALV | van der Bruggen et al. 1994a [126] | |
| *MAGE-A3* | A24 | TFPDLESEF | Oiso et al. 1999 [89] | |
| *MAGE-A3* | A24 | IMPKAGLLI | Tanaka et al. 1997 [111] | |
| *MAGE-A3* | B44 | MEVDPIGHLY | Herman et al. 1996 [48], Fleischhauer et al. 1996 [35] | |
| *MAGE-A3* | B52 | WQYFFPVIF | Russo et al. 2000 [103] | |
| *MAGE-A4* | A2 | GVYDGREHTV | Duffour et al. 1999 [33] | Melanoma, NSCLC, sarcomas, esophageal, colon and breast carcinomas [27] |
| *MAGE-A6* | A34 | MVKISGGPR | Zorn and Hercend, 1999b [147] | Melanoma, NSCLC, colon carcinoma, leukemias [27] |
| *MAGE-A10* | A2 | GLYDGMEHL | Huang et al. 1999 [52] | Not defined |
| *MAGE-A12* | Cw7 | VRIGHLYIL | Panelli et al. 2000 [91], Heidecker et al. 2000 [47] | Melanoma, myeloma, brain tumors, sarcoma, leukemias, SCLC, NSCLC, H/N tumors, bladder, lung, esophageal, breast, prostate and colorectal carcinoma [27] |
| *BAGE* | Cw16 | AARAVFLAL | Boël et al. 1995 [6] | Melanoma, bladder and mammary carcinomas, H/N SCC, NSCLC, sarcoma |
| *DAM-6, -10* | A2 | FLWGPRAYA | Fleischhauer et al. 1998 [36] | Melanoma, skin tumors, mammary and ovarian carcinomas [77] – lung carcinoma [25, 77] – seminomas [25] |
| *GAGE-1, -2, -8* | Cw6 | YRPRPRRY | Van den Eynde et al. 1995 [123], De Backer et al. 1999 [26] | Melanoma, sarcoma, NSCLC, SCLC, mesothelioma, sarcoma, seminoma, leukemias, lymphomas, H/N tumors, bladder, esophageal, mammary, colon, prostate carcinomas |
| *GAGE-3, -4, -5, -6, -7B* | A29 | YYWPRPRRY | De Backer et al. 1999 [26] | Melanomas, H/N tumors, leukemias, esophageal, lung and bladder carcinomas |
| *NA88-A* | B13 | MTQGQHFLQKV | Moreau-Aubry et al. 2000 [82] | Melanoma |
| *NY-ESO-1* | A2 | SLLMWITQCFL | Jäger et al. 1998 [54] | Melanoma, sarcoma, B-lymphomas, hepatoma, H/N tumors, bladder, lung, prostate, ovarian, thyroid and breast carcinoma [18] |
| *NY-ESO-1a (CAG-3)* | A2 | SLLMWITQC | Jäger et al. 1998 [54] | |
| | A2 | QLSLLMWIT | Jäger et al. 1998 [54] | |
| | A31 | ASGPGGGAPR | Wang et al. 1998b [134] | |

[a] Tissue distribution among tumors as described in the given references when different from the paper first reporting the sequence of the epitope

## Group 4: Class I HLA-restricted, tumor-specific antigens (Table 4)

Unique tumor antigens arise from point mutations of normal genes (like $\beta$-catenin, CDK4) [98, 137], whose molecular changes often accompany neoplastic transformation or progression. These antigens are thus expressed only in the individual tumor where they were identified, since it is unlikely that the same mutation may occur in two different neoplasms unless it involves genes (e.g. RAS) whose alteration is an obligatory step in neoplastic transformation.

**Table 2** Class I HLA-restricted melanocyte differentiation antigens. These antigens can only be expressed in normal and neoplastic cells of the same lineage (namely melanocytes, skin, retina, peripheral ganglia) or in normal cells of the prostate gland

| Gene | HLA allele | Peptide epitope | Authors [ref.] |
|---|---|---|---|
| *MART-1/Melan-A*[a] | A2 | AAGIGILTV | Coulie et al. 1994 [22], Kawakami et al. 1994a [58] |
| | A2 | EAAGIGILTV | Schneider et al. 1998 [106] |
| | A2 | ILTVILGVL | Castelli et al. 1995 [14] |
| | B45 | AEEAAGIGIL | Schneider et al. 1998 [106] |
| | B45 | AEEAAGIGILT | Schneider et al. 1998 [106] |
| *MC1R* | A2 | TILLGIFFL | Salazar-Onfray et al. 1997 [104] |
| | A2 | FLALIICNA | Salazar-Onfray et al. 1997 [104] |
| *Gp100* | A2 | KTWGQYWQV | Bakker et al. 1995 [3] |
| | A2 | AMLGTHTMEV | Tsai et al. 1997 [120] |
| | A2 | MLGTHTMEV | Tsai et al. 1997 [120] |
| | A2 | SLADTNSLAV | Tsai et al. 1997 [120] |
| | A2 | ITDQVPFSV | Kawakami et al. 1995 [61] |
| | A2 | LLDGTATLRL | Kawakami et al. 1994b [59] |
| | A2 | YLEPGPVTA | Cox et al. 1994 [24] |
| | A2 | VLYRYGSFSV | Kawakami et al. 1995 [61] |
| | A2 | RLMKQDFSV | Kawakami et al. 1998 [62] |
| | A2 | RLPRIFCSC | Kawakami et al. 1998 [62] |
| | A3 | LIYRRRLMK | Kawakami et al. 1998 [62] |
| | A3 | ALNFPGSQK | Kawashima et al. 1998 [65] |
| | A3 | SLIYRRRLMK | Kawashima et al. 1998 [65] |
| | A3 | ALLAVGATK | Skipper et al. 1996 [108] |
| | A24 | VYFFLPDHL | Robbins et al. 1997 [99] |
| | Cw8 | SNDGPTLI | Castelli et al. 1999 [15] |
| *PSA* | A1 | VSHSFPHPLY | Corman et al. 1998 [20] |
| | A2 | FLTPKKLQCV | Correale et al. 1997 [21] |
| | A2 | VISNDVCAQV | Correale et al. 1997 [21] |
| *PSM* | A1 | HSTNGVTRIY | Corman et al. 1998 [20] |
| *Tyrosinase* | A1 | KCDICTDEY | Kittlesen et al. 1998 [68] |
| | A1 | SSDYVIPIGTY | Kawakami et al. 1998 [62] |
| | A2 | YMDGTMSQV | Wölfel et al. 1994 [137] |
| | A2 | MLLAVLYCL | Wölfel et al. 1994 [137] |
| | A24 | AFLPWHRLF | Kang et al. 1995 [57] |
| | B44 | SEIWRDIDF | Brichard et al. 1996 [10] |
| *TRP-1 (or gp75)* | A31 | MSLQRQFLR | Wang et al. 1996b [132] |
| *TRP-2* | A2 | SVYDFFVWL | Parkhurst et al. 1998 [92] |
| | A2 | TLDSQVMSL | Noppen et al. 2000 [86] |
| | A31 | LLGPGRPYR | Wang et al. 1996a [131] |
| | A33 | LLGPGRPYR | Wang et al. 1998a [133] |
| | Cw8 | ANDPIFVVL | Castelli et al. 1999 [15] |

[a] Two different groups simultaneously discovered this gene and gave it two different names, MART-1 and Melan-A respectively

**Table 3** Class I HLA-restricted widely expressed antigens

| Gene | HLA | Peptide epitope | Tissue distribution | | Reference |
|---|---|---|---|---|---|
| | | | Tumors | Normal tissues | |
| *ART-4* | A24 | AFLRHAAL DYPSLSATDI | SCC, SCLC, H/N tumors, leukemia, lung, esophageal, gastric, cervical, endometrial, ovarian and breast carcinomas | Testis, placenta, fetal liver | Kawano et al. 2000 [64] |
| *CAMEL* | A2 | MLMAQEALAFL | Melanoma | Testis, placenta, heart, skeletal muscle, pancreas | Aarnoudse et al. 1999 [1] |
| *CEA* | A2 | YLSGANLNL (CAP-1)[a] | Melanoma | Testis, placenta, heart, skeletal muscle, pancreas | Tsang et al. 1995 [121] |
| *CEA* | A3 | HLFGYSWYK | Colon, rectum, pancreas, gastric, breast and lung carcinomas | Gastrointestinal embryonic tissue | Kawashima et al. 1999 [66] |
| *Cyp-B* | A24 | KFHRVIKDF DFMIQGGDF | Lung adenocarcinoma, T cell leukemia, lymphosarcoma – bladder, ovarian, uterine and esophageal SCC | Ubiquitously expressed in normal tissues | Gomi et al. 1999 [42] |

Table 3 (Continued)

| Gene | HLA | Peptide epitope | Tissue distribution | | Reference |
|---|---|---|---|---|---|
| | | | Tumors | Normal tissues | |
| *HER2/neu* | A2 | KIFGSLAFL | Melanoma – ovarian and breast carcinomas | Epithelial cells | Fisk et al. 1995 [34] |
| *HER2/neu* | A2 | IISAVVGIL | Melanoma, ovarian, pancreatic [96][b] and breast carcinomas | Epithelial cells | Peoples et al. 1995 [95] |
| *HER2/neu* | A2 | RLLQETELV | Melanoma, ovarian, gastric, pancreatic [96] and breast carcinomas | Epithelial cells | Kono et al. 1998 [71] |
| *HER2/neu* | A2 | VVLGVVFGI ILHNGAYSL YMIMVKCWMI | Melanoma, ovarian, gastric, pancreatic [96] and breast carcinomas | Epithelial cells | Rongcun et al. 1999 [101] |
| *HER2/neu* | A3 | VLRENTSPK | Melanoma, ovarian, gastric, pancreatic [96] and breast carcinomas | Epithelial cells | Kawashima et al. 1999 [66] |
| *hTERT*[c] | A2 | ILAKFLHWL | Lung and ovarian carcinomas – multiple myeloma, melanoma, sarcoma, acute leukemias, non-Hodgkin's lymphomas | Hematopoietic stem cells and progenitors; germinal center cells; basal keratinocytes; gonadal cells; certain proliferating epithelial cells | Vonderheide et al. 1999 [131] |
| *hTRT*[c] | A2 | ILAKFLHWL RLVDDFLLV | Lung, prostate and ovarian carcinomas, multiple myeloma, melanoma, sarcoma, acute leukemias, non-Hodgkin's lymphomas | Circulating B cells; germinal center B cells; thymocytes; CD34+ progenitor hemopoietic cells | Minev et al. 2000 [81] |
| *iCE* | B7 | SPRWWPTCL | RCC | Kidney, colon, small intestine, liver, heart, pituitary gland, adrenal gland, prostate, stomach | Ronsin et al. 1999 [102] |
| *MUC1* | A11 | STAPPAHGV | Breast and ovarian carcinomas, multiple myeloma, B-cell lymphoma | None[d] | Domenech et al. 1995 [31] |
| *MUC1* | A2 | STAPPVHNV | Breast and ovarian carcinoma, multiple myeloma, B-cell lymphoma | None[d] | Brossart et al. 1999 [11] |
| *MUC2* | A2 | LLNQLQVNL MLWGWREHV | Ovary, pancreas and breast mucinous tumors, colon carcinoma of non-mucinous type | Colon, small intestine, bronchus, cervix and gall bladder | Böhm et al. 1998 [7] |
| *PRAME* | A24 | LYVDSLFFL | Melanoma, H/N and lung SCC, NSCLC [122], RCC, adenocarcinoma, sarcoma, leukemias [122] | Testis, endometrium, ovary, adrenals, kidney, brain, skin | Ikeda et al. 1997 [53] |
| *P15* | A24 | AYGLDFYIL | Melanoma | Testis, spleen, thymus, liver, kidney, adrenal tissue, lung tissue, retinal tissue | Robbins et al. 1995 [97] |
| *RU1* | B51 | VPYGSFKHV | Melanoma, renal and bladder carcinomas | Testis, kidney, heart, skin, brain, ovary, liver, lung, lymphocytes, thymus, fibroblasts | Morel et al. 2000 [83] |
| | B7 | LPRWPPPQL | Melanoma, sarcomas leukemia – brain, esophageal and H/N tumors – renal, colon, thyroid, mammary, bladder, prostatic and lung carcinomas | Testis, kidney, liver, urinary bladder | Van den Eynde et al. 1999 [124] |
| *SART-1* | A24 | EYRGFTQDF | Esophageal, H/N and lung SCC – adenocarcinoma, uterine cancer | Testis, fetal liver | Kikuchi et al. 1999 [67] |
| *SART-1* | A*2601 | KGSGKMKTE | Esophageal, H/N and lung SCC, adenocarcinoma, uterine cancer | Testis, fetal liver | Shichijo et al. 1998 [107] |
| *SART-3* | A24 | VYDYNCHVDL AYIDFEMKI | H/N, esophageal and lung SCC, adenocarcinoma, leukemia, melanoma | Lymphoid cells, fibroblasts, testis, fetal liver | Yang et al. 1999 [139] |
| *WT1* | A2 | RMFPNAPYL | Gastric, colon, lung, breast, ovary, uterine, thyroid and hepatocellular carcinomas – leukemia (including AML, ALL and CML) | Kidney, ovary, testis, spleen | Oka et al. 2000 [90] |

[a] CAP-1 is an alternative name of this peptide
[b] Tissue distribution among tumors as described in the given references when different from the paper first reporting the sequence of the epitope
[c] Telomerase is expressed in most human tumors: those listed were shown to be susceptible to lysis by cytotoxic T lymphocytes
[d] All epithelial tissues express mucin-like hyperglycosylated molecules

**Table 4** Class I HLA-restricted tumor-specific antigens, including both unique (CDK-4, MUM-1, MUM-2, β-catenin, HLA-A2-R170I, ELF2 m, myosin-m, caspase-8, KIAA0205, HSP70-2m) and shared (CAMEL, TRP-2/INT2, GnT-V, G 250) antigens

| Gene | HLA allele | Peptide epitope | Tissue distribution | | Reference |
|---|---|---|---|---|---|
| | | | Tumors | Normal tissues | |
| *AFP* | A2 | GVALQTMKQ | Hepatocellular carcinoma | Fetal liver | Butterfield et al. 1999 [12] |
| *β-Catenin/m* | A24 | SYLDSGIHF | Melanoma | None | Robbins et al. 1996 [98] |
| *Caspase-8/m* | B35 | FPSDSWCYF | H/N tumors | None | Mandruzzato et al. 1997 [78] |
| *CDK-4/m* | A2 | ACDPHSGHFV | Melanoma | None | Wölfel et al. 1995 [138] |
| *ELF2 M* | A68 | ETVSEQSNV | Lung SCC | None | Hogan et al. 1998 [50] |
| *GnT-V* | A2 | VLPDVFIRC(V)[a] | Melanoma, brain tumors, sarcoma | Breast and brain (low expression) | Guilloux et al. 1996 [45] |
| *G250* | A2 | HLSTAFARV | RCC, colon, ovarian and cervical carcinomas | None | Vissers et al. 1999 [129] |
| *HSP70-2M* | A2 | SLFEGIDIY | RCC, melanoma, neuroblastoma | None | Gaudin et al. 1999 [39] |
| *HA-A*0201-R170I* | A2 | CVEWLRIYLENGK | RCC | None | Brändle et al. 1996 [9] |
| *HST-2* | A31 | YSWMDISCWI | Gastric signet cell carcinoma | None | Suzuki et al. 1999 [109] |
| *KIAA0205* | B44*03 | AEPINIQTV | Bladder cancer | None | Gueguen et al. 1998 [44] |
| *MUM-1* | B44 | EEKLIVVLF | Melanoma | None | Coulie et al. 1995 [23] |
| *MUM-2* | B44 | SELFRSGLDY | Melanoma | None | Chiari et al. 1999 [19] |
| *MUM-2* | Cw6 | FRSGLDSYV | Melanoma | None | Chiari et al. 1999 [19] |
| *MUM-3* | A28 | EAFIQPITR | Melanoma | None | Baurain et al. 2000 [4] |
| *Myosin/m* | A3 | KINKNPKYK | Melanoma | None | Zorn and Hercend, 1999a [146] |
| *RAGE* | B7 | SPSSNRIRNT | Melanoma, sarcomas, mesotheliomas, H/N tumors, bladder, renal, colon and mammary carcinomas | Retina only | Gaugler et al. 1996 [41] |
| *SART-2* | A24 | DYSARWNEI | H/N and lung SCC, lung adenocarcinoma, RCC, melanoma, brain tumors, esophageal and uterine cancers | None | Nakao et al. 2000 [85] |
| | | AYDFLYNYL | | | |
| | | SYTRLFLIL | | | |
| *TRP-2/INT2* | A68 | EVISCKLIKR | Melanoma | None | Lupetti et al. 1998 [76] |
| *707-AP* | A2 | RVAALARDA | Melanoma | None[b] | Morioka et al. 1995 [84] |

[a] VLPDVFIRC(V) = nonamer and decamer peptides are both recognized by CTLs
[b] This antigen is not expressed in normal cells but, as the tissue of the testis was not tested, it will not become clear to which category the antigen may belong until more information is available

In mouse models unique antigens have been shown to be more immunogenic than the other groups of shared antigens [32]; since unique antigens are responsible for the rejection of tumor transplants in mice, they have been defined as tumor-specific transplantation antigens (TSTA). The unique antigens are the most specific targets for immunotherapy, but this potential advantage must be balanced against the almost total impossibility of their clinical use, as they can induce an immune response only against the original tumor on which they were found.

Other tumor-specific but shared antigens have been described which are generated by alteration in splicing mechanisms and which occur in tumor but not in normal cells, as in the case of TRP-2/INT2 [76].

## Group 5: Class II HLA-restricted antigens (Table 5)

Stimulation of the CD4+ T helper cells by tumor antigens is considered to be impaired or absent in cancer patients and this may be the reason of an insufficient immune response to tumors. Therefore the identification of tumor antigen epitopes recognized by such lymphocytes is a crucial step in the long sought improvement of antitumor immune response that may result into clinical efficacy. The first epitope presented by a class II HLA and capable of provoking a CD4+ T-cell response was identified in 1994 in melanoma tyrosinase [117]. Then a gap of 4 years followed during which only one additional epitope was characterized [118], before other genes encoding class II-restricted peptides were discovered. However, as the technical and methodological approaches for identifying CD4+ T-cell epitopes of tumor antigens have become available, an exponential increase in reporting such epitopes has been seen. In fact, since 1998 as many as 27 new class II HLA-restricted epitopes from 14 antigens have been molecularly identified using, among others, Ii-cDNA fusion libraries [135], immunized transgenic mice [145] and biochemical approaches [96].

Table 5 Class II HLA-restricted antigens

| Gene | HLA allele | Peptide epitope | Tissue distribution: Tumors | Tissue distribution: Normal tissues | Reference |
|---|---|---|---|---|---|
| Epitopes from normal protein antigens | | | | | |
| *Annexin II* | DRB*0401 | DVPKWISIM-TERSVPH | Melanoma | Not done | Li et al. 1998 [73] |
| *Gp100* | DRB1*0401 | WNRQLYPE-WTEAQRLD | Melanoma | Melanocytes | Li et al. 1998 [73] |
| *MAGE-1, -2, -3, -6* | DRB*1301 DRB*1302 | LLKYRAREP-VTKAE | Melanoma, lung and breast carcinomas, H/N SCC | Testis, placenta | Chaux et al. 1999a [16] |
| *MAGE-3* | DR*1101 | TSYVKVLHHM-VKISG | Melanoma, lung and breast carcinomas, H/N SCC | Testis, placenta | Manici et al. 1999 [79] |
| *MAGE-3* | DRB*1301 DRB*1302 | AELVHFLLLK-YRAR | Melanoma, lung and breast carcinomas, H/N SCC | Testis, placenta | Chaux et al. 1999b [17] |
| *MART-1/Melan-A* | DRB1*0401 | RNGYRALMDKS-LHVGTQCALTRR | Melanoma | Melanocytes | Zarour et al. 2000 [143] |
| *MUC1* | DR3 | PGSTAPPAHGVT | Breast and ovarian cancers, multiple myeloma, B-cell lymphoma | None[a] | Hiltbold et al. 1998 [49] |
| *NY-ESO-1* | DRB4*0101 | VLLKEFTVSG | Melanoma, B-lymphoma, hepatoma [18][b], sarcoma, H/N tumors, – bladder, lung, prostate, ovarian, thyroid and breast carcinomas | Testis | Zeng et al. 2000 [145] |
| *NY-ESO-1* | DRB4*0101–0103 | PLPVPGVLLK-EFTVSGNI VLLKEFTVSG-NILTIRLT AADHRQLQL-SISSCLQQL | B-lymphoma, melanoma, sarcoma, H/N tumors, hepatoma [18] – bladder, lung, prostate, ovarian, thyroid and breast carcinomas | Testis | Jäger et al. 2000 [55] |
| *PSA* | DR4 | ILLGRMSLFM-PEDTG SLFHPEDTGQVFQ QVFQVSHSFPHPLYD NDLMLLRLSEPAELT KKLQCVQLHVISM GVLQGITSMGSEPCA | Melanoma | Melanocytes | Corman et al. 1998 [20] |
| *Tyrosinase* | DRB1*0401 | QNILLSNAPLGPQFP DYSYLQDSDPD-SFQD SYLQDSDPDSFQD | Melanoma | Melanocytes | Topalian et al. 1994 [117], Topalian et al. 1996 [118] |
| *Tyrosinase* | DRB1*1501 | RHRPLQEVYP-EANAPIGHNRE | Melanoma | Melanocytes | Kobayashi et al. 1998a [69] |
| *Tyrosinase* | DRB1*0405 | EIWRDIDFAHE | Melanoma | Melanocytes | Kobayashi et al. 1998b [70] |
| Epitopes from mutated protein antigens | | | | | |
| *HPV-E7* | DR*0401 DR*0407 | LFMDTLSFVCPLC LFMDSLNFVCPWC | Cervical carcinoma | None | Höhn et al. 1999 [51] |
| *CDC27/m* | DRB1*0401 | FSWAMDLDPKGA | Melanoma | None | Wang et al. 1999a [135] |
| *TPI/m* | DRB1*0101 | GELIGILNAAKVPAD | Melanoma | None | Pieper et al. 1999 [96] |

[a] All epithelial tissues express highly glycosilated mucins whereas tumor cells often show hypoglycosilated mucins with a normal protein sequence

[b] Tissue distribution among tumors as described in the given references when different from the paper first reporting the sequence of the epitope

It is of note that even class II-restricted antigens include a subgroup of mutated proteins which, therefore, represent truly tumor-specific antigens.

## Group 6: Fusion proteins (Table 6)

In several malignancies, particularly in some forms of leukemia, the molecular mechanism of carcinogenesis involves translocation of chromosomes which results in fusion of distant genes. This often causes the synthesis of fusion proteins which characterize each type of disease (e.g., bcr-abl and pml-RARα in CML and APL, respectively) and generate new epitopes that can be recognized by T cells, either CD8+ or CD4+ in class I or class II HLA restriction, respectively. Although these epitopes appear to be weakly immunogenic in leukemia patients [28], some of these peptides or proteins

Table 6 Epitopes derived from fusion proteins (fusion proteins are never found in normal tissues)

| Gene | HLA allele | Peptide epitope | Tissue distribution among tumors | Reference |
|---|---|---|---|---|
| HLA class I restricted epitopes | | | | |
| *bcr-abl*[a] | A2 | FMVELVEGA<br>KLSEQESLL<br>MLTNSCVKL | CML | Buzyn et al. 1997 [13] |
| *bcr-abl p210(b3a2)* | A2 | SSKALQRPV | CML | Yotnda et al. 1998a [141] |
| *bcr-abl (b3a2)* | A3 | ATGFKQSSK<br>KQSSKALQR | CML | Greco et al. 1996 [43] |
| *bcr-abl p210 (b3a2)* | A3, A11 | HSATGFKQSSK | CML | Bocchia et al. 1996 [5] |
| *bcr-abl p210(b3a2)* | A3 | KQSSKALQR | CML | Norbury et al. 2000 [87] |
| *bcr-abl p210(b3a2)* | B8 | GFKQSSKAL | CML | Norbury et al. 2000 [87] |
| *ETV6/AML* | A2 | RIAECILGM | ALL | Yotnda et al. 1998b [142] |
| HLA class II restricted epitopes | | | | |
| *bcr-abl p190 (e1a2)* | DRB1*1501 | EGAFHGDAEALQRPVAS | ALL | Tanaka et al. 2000 [112] |
| *bcr-abl p210 (b2a2)* | DRB5*0101 | IPLTINKEEALQRPVAS | CML | ten Bosch et al. 1999 [116] |
| *bcr-abl p210 (b3a2)* | DRB1*0401 | ATGFKQSSKALQRPVAS | CML | ten Bosch et al. 1996 [115] |
| *bcr-abl p210 (b3a2)* | DRB1*1501 | ATGFKQSSKALQRPVAS | CML | ten Bosch et al. 1996 [115] |
| *bcr-abl (b3a2)* | DRB1*0901 | ATGFKQSSKALQRPVAS | CML | Yasukawa et al. 1998 [140] |
| *bcr-abl (b3a2)* | DRB1*1101 | LIVVIVHSATGFKQSS-KALQRPVA | CML | Pawelec et al. 1996 [93] |
| *bcr-abl (b3a2)* | DR11 | IVHSATGFKQSSKALQRP-VASDFEP | CML | Bocchia et al. 1996 [5] |
| *Dek-cain* | DRB4*0103 | TMKQICKKEIRRLHQY | AML | Ohminami et al. 1999 [88] |
| *LDLR/FUT* | DRB1*0101 | GGAPPVTWRRAPAPG<br>WRRAPAPGAKAMAPG | Melanoma | Wang et al. 1999b [132] |
| *Pml/RARα* | DR11 | NSNHVASGA-GEAAIETQSSSSEEIV [28] | APL | Gambacorti-Passerini et al. 1993 [38] |
| *p190 minor bcr-abl (e1a2)* | DRB1*1501 | EGAFHGDAEALQRPVAS | AML | Tanaka et al. 2000 [112] |
| *TEL/AML1* | DP5, DP17 | IGRIAECILGMNPSR | AML | Yun et al. 1999 [143] |

[a]These bcr-abl epitopes are not true fusion proteins generated-epitopes, because they derive from outside the bcr-abl junction

Table 7 Frequency of epitopes recognized by a given HLA allele

| Antigen | No. of epitopes | HLA-A | HLA-B | HLA-C |
|---|---|---|---|---|
| MAGE-1, -2, -3, -4, -6, -10, -12 | 24 | 13 (54%) | 7 (29% | 4 (17%) |
| GAGE-1, -2, -3, -4, -5, -6, -7B, -8 | 8 | 5 (62.5%) | 0 | 3 (37.5%) |
| MART-1 | 6 | 4 (67%) | 2 (33%) | 0 |
| Gp100 | 12 | 11 (92%) | 0 | 1 (8%) |
| Tyrosinase | 6 | 5 (83%) | 1 (17%) | 0 |

can nevertheless be used to pulse dendritic cells for vaccination.

### Frequency of epitopes recognized by a given HLA allele (Table 7)

In Table 7 we have summarized, for those antigens from which a high number of epitopes have been described (e.g., CT and differentiation antigens of melanoma) the distribution of epitopes recognized in the context of different HLA loci. This table shows that the majority of epitopes are seen as restricted by HLA-A in all the three groups of antigens considered. Whether this reflects a bias caused by the fact that most of the studies have been carried out with HLA-A-restricted T cells or is mediated by the immunodominant role of the HLA locus in recognition of tumor antigens remains to be established.

## Conclusions

Several excellent and timely reviews on tumor antigens have been published periodically during the past few years [8, 63, 100]. However, to our knowledge a comprehensive list of all available tumor antigens and their epitopes and HLA restriction has never been reported, despite the fact that the features of each antigen can be easily found in data bases. We hope that our work may be of interest for many tumor immunologists and students. Needless to say, we may have inadvertently missed information on some antigens despite our careful scrutiny of the published literature; therefore, we will be grateful to any readers who provide us with any missing information. We now plan to update these tables bimonthly in order to keep our data base as informative as possible. The antigen list can also be found at the INT website (www.istitutotumori.mi.it).

**Acknowledgements** The authors would like to thank Ms Grazia Barp for editorial assistance. This work was supported in part by a grant of the European Community (QLK3-1999-00064).

## References


1. Aarnoudse CA, van den Doel PB, Heemskerk B, Schrier PI (1999) Interleukin-2-induced, melanoma-specific T cells recognize CAMEL, an unexpected translation product of LAGE-1. Int J Cancer 82: 442
2. Anichini A, Maccalli C, Mortarini R, Salvi S, Mazzocchi A, Squarcina P, Herlyn M, Parmiani G (1993) Melanoma cells and normal melanocytes share antigens recognized by HLA-A2-restricted cytotoxic T cell clones from melanoma patients. J Exp Med 177: 989
3. Bakker AB, Schreurs MW, Tafazzul G, de Boer AJ, Kawakami Y, Adema GJ, Figdor CG (1995) Identification of a novel peptide derived from the melanocyte-specific gp100 antigen as the dominant epitope recognized by an HLA-A2.1-restricted anti-melanoma CTL line. Int J Cancer 62: 97
4. Baurain JF, Colau D, van Baren N, Landry C, Martelange V, Vikkula M, Boon T, Coulie PG (2000) High frequency of autologous anti-melanoma CTL directed against an antigen generated by a point mutation in a new helicase gene. J Immunol 164: 6057
5. Bocchia M, Korontsvit T, Xu Q, Mackinnon S, Yang SY, Sette A, Scheinberg DA (1996) Specific human cellular immunity to bcr-abl oncogene-derived peptides. Blood 87: 3587
6. Boel P, Wildmann C, Sensi ML, Brasseur R, Renauld JC, Coulie P, Boon T, van der Bruggen P (1995) BAGE: a new gene encoding an antigen recognized on human melanomas by cytolytic T lymphocytes. Immunity 2: 167
7. Bohm CM, Hanski ML, Stefanovic S, Rammensee HG, Stein H, Taylor-Papadimitriou J, Riecken EO, Hanski C (1998) Identification of HLA-A2-restricted epitopes of the tumor-associated antigen MUC2 recognized by human cytotoxic T cells. Int J Cancer 75: 688
8. Boon T, van der Bruggen P (1996) Human tumor antigens recognized by T lymphocytes. J Exp Med 183: 725
9. Brandle D, Brasseur F, Weynants P, Boon T, Van den Eynde B (1996) A mutated HLA-A2 molecule recognized by autologous cytotoxic T lymphocytes on a human renal cell carcinoma. J Exp Med 183: 2501
10. Brichard VG, Herman J, Van Pel A, Wildmann C, Gaugler B, Wolfel T, Boon T, Lethe B (1996) A tyrosinase nonapeptide presented by HLA-B44 is recognized on a human melanoma by autologous cytolytic T lymphocytes. Eur J Immunol 26: 224
11. Brossart P, Heinrich KS, Stuhler G, Behnke L, Reichardt VL, Stevanovic S, Muhm A, Rammensee HG, Kanz L, Brugger W (1999) Identification of HLA-A2-restricted T-cell epitopes derived from the MUC1 tumor antigen for broadly applicable vaccine therapies. Blood 93: 4309
12. Butterfield LH, Koh A, Meng W, Vollmer CM, Ribas A, Dissette V, Lee E, Glaspy JA, McBride WH, Economou JS (1999) Generation of human T-cell responses to an HLA-A2.1-restricted peptide epitope derived from alpha-fetoprotein. Cancer Res 59: 3134
13. Buzyn A, Ostankovitch M, Zerbib A, Kemula M, Connan F, Varet B, Guillet JG, Choppin J (1997) Peptides derived from the whole sequence of BCR-ABL bind to several class I molecules allowing specific induction of human cytotoxic T lymphocytes. Eur J Immunol 27: 2066
14. Castelli C, Storkus WJ, Maeurer MJ, Martin DM, Huang EC, Pramanik BN, Nagabhushan TL, Parmiani G, Lotze MT (1995) Mass spectrometric identification of a naturally processed melanoma peptide recognized by CD8+ cytotoxic T lymphocytes. J Exp Med 181: 363
15. Castelli C, Tarsini P, Mazzocchi A, Rini F, Rivoltini L, Ravagnani F, Gallino F, Belli F, Parmiani G (1999) Novel HLA-Cw8-restricted T cell epitopes derived from tyrosinase-related protein-2 and gp100 melanoma antigens. J Immunol 162: 1739
16. Chaux P, Luiten R, Demotte N, Vantomme V, Stroobant V, Traversari C, Russo V, Schultz E, Cornelis GR, Boon T, van der Bruggen P (1999a) Identification of five MAGE-A1 epitopes recognized by cytolytic T lymphocytes obtained by in vitro stimulation with dendritic cells transduced with MAGE-A1. J Immunol 163: 2928
17. Chaux P, Vantomme V, Stroobant V, Thielemans K, Corthals J, Luiten R, Eggermont AM, Boon T, van der Bruggen P (1999b) Identification of MAGE-3 epitopes presented by HLA-DR molecules to CD4(+) T lymphocytes. J Exp Med 189: 767
18. Chen YT, Scanlan MJ, Sahin U, Tureci O, Gure AO, Tsang S, Williamson B, Stockert E, Pfreundschuh M, Old LJ (1997) A testicular antigen aberrantly expressed in human cancers detected by autologous antibody screening. Proc Natl Acad Sci USA 94: 1914
19. Chiari R, Foury F, De Plaen E, Baurain JF, Thonnard J, Coulie PG (1999) Two antigens recognized by autologous cytolytic T lymphocytes on a melanoma result from a single point mutation in an essential housekeeping gene. Cancer Res 59: 5785
20. Corman JM, Sercarz EE, Nanda NK (1998) Recognition of prostate-specific antigenic peptide determinants by human CD4 and CD8 T cells. Clin Exp Immunol 114: 166
21. Correale P, Walmsley K, Nieroda C, Zaremba S, Zhu M, Schlom J, Tsang KY (1997) In vitro generation of human cytotoxic T lymphocytes specific for peptides derived from prostate-specific antigen. J Natl Cancer Inst 89: 293
22. Coulie PG, Brichard V, Van Pel A, Wolfel T, Schneider J, Traversari C, Mattei S, De Plaen E, Lurquin C, Szikora JP, Renauld JC, Boon T (1994) A new gene coding for a differentiation antigen recognized by autologous cytolytic T lymphocytes on HLA-A2 melanomas. J Exp Med 180: 35
23. Coulie PG, Lehmann F, Lethe B, Herman J, Lurquin C, Andrawiss M, Boon (1995) A mutated intron sequence codes for an antigenic peptide recognized by cytolytic T lymphocytes on a human melanoma. Proc Natl Acad Sci USA 92: 7976
24. Cox AL, Skipper J, Chen Y, Henderson RA, Darrow TL, Shabanowitz J, Engelhard VH, Hunt DF, Slingluff CL Jr (1994) Identification of a peptide recognized by five melanoma-specific human cytotoxic T cell lines. Science 264: 716
25. Dabovic B, Zanaria E, Bardoni B, Lisa A, Bordignon C, Russo V, Matessi C, Traversari C, Camerino G (1995) A family of rapidly evolving genes from the sex reversal critical region in Xp21. Mamm Genome 6: 571
26. De Backer O, Arden KC, Boretti M, Vantomme V, De Smet C, Czekay S, Viars CS, De Plaen E, Brasseur F, Chomez P, Van den Eynde B, Boon T, van der Bruggen P (1999) Characterization of the GAGE genes that are expressed in various human cancers and in normal testis. Cancer Res 59: 3157
27. De Plaen E, Arden K, Traversari C, Gaforio JJ, Szikora JP, De Smet C, Brasseur F, van der Bruggen P, Lethe B, Lurquin C, Brasseur R, Chomez P, De Backer O, Cavenee W, Boon T (1994) Structure, chromosomal localization, and expression of 12 genes of the MAGE family. Immunogenetics 40: 360
28. Dermime S, Bertazzoli C, Marchesi E, Ravagnani F, Blaser K, Corneo GM, Pogliani E, Parmiani G, Gambacorti-Passerini C (1996) Lack of T-cell-mediated recognition of the fusion region of the pml/RAR-alpha hybrid protein by lymphocytes of acute promyelocytic leukemia patients. Clin Cancer Res 2: 593
29. De Smet C, Lurquin C, van der Bruggen P, De Plaen E, Brasseur F, Boon T (1994) Sequence and expression pattern of the human MAGE2 gene. Immunogenetics 39: 121
30. De Smet C, Lurquin C, Lethe B, Martelange V, Boon T (1999) DNA methylation is the primary silencing mechanism for a set of germ line- and tumor-specific genes with a CpG-rich promoter. Mol Cell Biol 19: 7327
31. Domenech N, Henderson RA, Finn OJ (1995) Identification of an HLA-A11-restricted epitope from the tandem repeat

domain of the epithelial tumor antigen mucin. J Immunol 155: 4766
32. Dudley ME, Roopenian DC (1996) Loss of a unique tumor antigen by cytotoxic T lymphocyte immunoselection from a 3-methylcholanthrene-induced mouse sarcoma reveals secondary unique and shared antigens. J Exp Med 184: 441
33. Duffour MT, Chaux P, Lurquin C, Cornelis G, Boon T, van der Bruggen P (1999) A MAGE-A4 peptide presented by HLA-A2 is recognized by cytolytic T lymphocytes. Eur J Immunol 29: 3329
34. Fisk B, Blevins TL, Wharton JT, Ioannides CG (1995) Identification of an immunodominant peptide of HER-2/neu protooncogene recognized by ovarian tumor-specific cytotoxic T lymphocyte lines. J Exp Med 181: 2109
35. Fleischhauer K, Fruci D, Van Endert P, Herman J, Tanzarella S, Wallny HJ, Coulie P, Bordignon C, Traversari C (1996) Characterization of antigenic peptides presented by HLA-B44 molecules on tumor cells expressing the gene MAGE-3. Int J Cancer 68: 622
36. Fleischhauer K, Gattinoni L, Dalerba P, Lauvau G, Zanaria E, Dabovic B, van Endert PM, Bordignon C, Traversari C (1998) The DAM gene family encodes a new group of tumor-specific antigens recognized by human leukocyte antigen A2-restricted cytotoxic T lymphocytes. Cancer Res 58: 2969
37. Fujie T, Tahara K, Tanaka F, Mori M, Takesako K, Akiyoshi T (1999) A MAGE-1-encoded HLA-A24-binding synthetic peptide induces specific anti-tumor cytotoxic T lymphocytes. Int J Cancer 80: 169
38. Gambacorti-Passerini C, Grignani F, Arienti F, Pandolfi PP, Pelicci PG, Parmiani G (1993) Human CD4 lymphocytes specifically recognize a peptide representing the fusion region of the hybrid protein pml/RAR alpha present in acute promyelocytic leukemia cells. Blood 81: 1369
39. Gaudin C, Kremer F, Angevin E, Scott V, Triebel F (1999) A hsp70–2 mutation recognized by CTL on a human renal cell carcinoma. J Immunol 162: 1730
40. Gaugler B, Van den Eynde B, van der Bruggen P, Romero P, Gaforio JJ, De Plaen E, Lethe B, Brasseur F, Boon T (1994) Human gene MAGE-3 codes for an antigen recognized on a melanoma by autologous cytolytic T lymphocytes. J Exp Med 179: 921
41. Gaugler B, Brouwenstijn N, Vantomme V, Szikora JP, Van der Spek CW, Patard JJ, Boon T, Schrier P, Van den Eynde BJ (1996) A new gene coding for an antigen recognized by autologous cytolytic T lymphocytes on a human renal carcinoma. Immunogenetics 44: 323
42. Gomi S, Nakao M, Niiya F, Imamura Y, Kawano K, Nishizaka S, Hayashi A, Sobao Y, Oizumi K, Itoh K (1999) A cyclophilin B gene encodes antigenic epitopes recognized by HLA-A24-restricted and tumor-specific CTLs. J Immunol 163: 4994
43. Greco G, Fruci D, Accapezzato D, Barnaba V, Nisini R, Alimena G, Montefusco E, Vigneti E, Butler R, Tanigaki N, Tosi R (1996) Two brc-abl junction peptides bind HLA-A3 molecules and allow specific induction of human cytotoxic T lymphocytes. Leukemia 10: 693
44. Gueguen M, Patard JJ, Gaugler B, Brasseur F, Renauld JC, Van Cangh PJ, Boon T, Van den Eynde BJ (1998) An antigen recognized by autologous CTLs on a human bladder carcinoma. J Immunol 160: 6188
45. Guilloux Y, Lucas S, Brichard VG, Van Pel A, Viret C, De Plaen E, Brasseur F, Lethe B, Jotereau F, Boon T (1996) A peptide recognized by human cytolytic T lymphocytes on HLA-A2 melanomas is encoded by an intron sequence of the N-acetylglucosaminyltransferase V gene. J Exp Med 183: 1173
46. Gure AO, Stockert E, Arden KC, Boyer AD, Viars CS, Scanlan MJ, Old LJ, Chen YT (2000) CT10: a new cancer-testis (CT) antigen homologous to CT7 and the MAGE family, identified by representational-difference analysis. Int J Cancer 85: 726
47. Heidecker L, Brasseur F, Probst-Kepper M, Gueguen M, Boon T, Van den Eynde BJ (2000) Cytolytic T lymphocytes raised against a human bladder carcinoma recognize an antigen encoded by gene MAGE-A12. J Immunol 164: 6041
48. Herman J, van der Bruggen P, Luescher IF, Mandruzzato S, Romero P, Thonnard J, Fleischhauer K, Boon T, Coulie PG (1996) A peptide encoded by the human MAGE3 gene and presented by HLA-B44 induces cytolytic T lymphocytes that recognize tumor cells expressing MAGE3. Immunogenetics 43: 377
49. Hiltbold EM, Ciborowski P, Finn OJ (1998) Naturally processed class II epitope from the tumor antigen MUC1 primes human CD4+ T cells. Cancer Res 58: 5066
50. Hogan KT, Eisinger DP, Cupp SB 3rd, Lekstrom KJ, Deacon DD, Shabanowitz J, Hunt DF, Engelhard VH, Slingluff CL Jr, Ross MM (1998) The peptide recognized by HLA-A68.2-restricted, squamous cell carcinoma of the lung-specific cytotoxic T lymphocytes is derived from a mutated elongation factor 2 gene. Cancer Res 58: 5144
51. Hohn H, Pilch H, Gunzel S, Neukirch C, Hilmes C, Kaufmann A, Seliger B, Maeurer MJ (1999) CD4+ tumor-infiltrating lymphocytes in cervical cancer recognize HLA-DR-restricted peptides provided by human papillomavirus-E7. J Immunol 163: 5715
52. Huang LQ, Brasseur F, Serrano A, De Plaen E, van der Bruggen P, Boon T, Van Pel A (1999) Cytolytic T lymphocytes recognize an antigen encoded by MAGE-A10 on a human melanoma. J Immunol 162: 6849
53. Ikeda H, Lethe B, Lehmann F, van Baren N, Baurain JF, de Smet C, Chambost H, Vitale M, Moretta A, Boon T, Coulie PG (1997) Characterization of an antigen that is recognized on a melanoma showing partial HLA loss by CTL expressing an NK inhibitory receptor. Immunity 6: 199
54. Jager E, Chen YT, Drijfhout JW, Karbach J, Ringhoffer M, Jager D, Arand M, Wada H, Noguchi Y, Stockert E, Old LJ, Knuth A (1998) Simultaneous humoral and cellular immune response against cancer-testis antigen NY-ESO-1: definition of human histocompatibility leukocyte antigen (HLA)-A2-binding peptide epitopes. J Exp Med 187: 265
55. Jager E, Jager D, Karbach J, Chen YT, Ritter G, Nagata Y, Gnjatic S, Stockert E, Arand M, Old LJ, Knuth A (2000) Identification of NY-ESO-1 epitopes presented by human histocompatibility antigen (HLA)-DRB4*0101–0103 and recognized by CD4(+) T lymphocytes of patients with NY-ESO-1-expressing melanoma. J Exp Med 191: 625
56. Jassim A, Ollier W, Payne A, Biro A, Oliver RT, Festenstein H (1989) Analysis of HLA antigens on germ cells in human semen. Eur J Immunol 19: 1215
57. Kang X, Kawakami Y, el-Gamil M, Wang R, Sakaguchi K, Yannelli JR, Appella E, Rosenberg SA, Robbins PF (1995) Identification of a tyrosinase epitope recognized by HLA-A24-restricted, tumor-infiltrating lymphocytes. J Immunol 155: 1343
58. Kawakami Y, Eliyahu S, Delgado CH, Robbins PF, Rivoltini L, Topalian SL, Miki T, Rosenberg SA (1994a) Cloning of the gene coding for a shared human melanoma antigen recognized by autologous T cells infiltrating into tumor. Proc Natl Acad Sci USA 91: 3515
59. Kawakami Y, Eliyahu S, Delgado CH, Robbins PF, Sakaguchi K, Appella E, Yannelli JR, Adema GJ, Miki T, Rosenberg SA (1994b) Identification of a human melanoma antigen recognized by tumor-infiltrating lymphocytes associated with in vivo tumor rejection. Proc Natl Acad Sci USA 91: 6458
60. Kawakami Y, Eliyahu S, Sakaguchi K, Robbins PF, Rivoltini L, Yannelli JR, Appella E, Rosenberg SA (1994c) Identification of the immunodominant peptides of the MART-1 human melanoma antigen recognized by the majority of HLA-A2-restricted tumor infiltrating lymphocytes. J Exp Med 180: 347
61. Kawakami Y, Eliyahu S, Jennings C, Sakaguchi K, Kang X, Southwood S, Robbins PF, Sette A, Appella E, Rosenberg SA (1995) Recognition of multiple epitopes in the human mela-

noma antigen gp100 by tumor-infiltrating T lymphocytes associated with in vivo tumor regression. J Immunol 154: 3961
62. Kawakami Y, Robbins PF, Wang X, Tupesis JP, Parkhurst MR, Kang X, Sakaguchi K, Appella E, Rosenberg SA (1998) Identification of new melanoma epitopes on melanosomal proteins recognized by tumor infiltrating T lymphocytes restricted by HLA-A1, -A2, and -A3 alleles. J Immunol 161: 6985
63. Kawakami Y, Rosenberg SA (1997) Human tumor antigens recognized by T-cells. Immunol Res 16: 313
64. Kawano K, Gomi S, Tanaka K, Tsuda N, Kamura T, Itoh K, Yamada A (2000) Identification of a new endoplasmic reticulum-resident protein recognized by HLA-A24-restricted tumor-infiltrating lymphocytes of lung cancer. Cancer Res 60: 3550
65. Kawashima I, Tsai V, Southwood S, Takesako K, Celis E, Sette A (1998) Identification of gp100-derived, melanoma-specific cytotoxic T-lymphocyte epitopes restricted by HLA-A3 supertype molecules by primary in vitro immunization with peptide-pulsed dendritic cells. Int J Cancer 78: 518
66. Kawashima I, Tsai V, Southwood S, Takesako K, Sette A, Celis E (1999) Identification of HLA-A3-restricted cytotoxic T lymphocyte epitopes from carcinoembryonic antigen and HER-2/neu by primary in vitro immunization with peptide-pulsed dendritic cells. Cancer Res 59: 431
67. Kikuchi M, Nakao M, Inoue Y, Matsunaga K, Shichijo S, Yamana H, Itoh K (1999) Identification of a SART-1-derived peptide capable of inducing HLA-A24-restricted and tumor-specific cytotoxic T lymphocytes. Int J Cancer 81: 459
68. Kittlesen DJ, Thompson LW, Gulden PH, Skipper JC, Colella TA, Shabanowitz J, Hunt DF, Engelhard VH, Slingluff CL Jr, Shabanowitz JA (1998) Human melanoma patients recognize an HLA-A1-restricted CTL epitope from tyrosinase containing two cysteine residues: implications for tumor vaccine development [published erratum appears in J Immunol 1999; 162(5): 3106]. J Immunol 160: 2099
69. Kobayashi H, Kokubo T, Sato K, Kimura S, Asano K, Takahashi H, Iizuka H, Miyokawa N, Katagiri M (1998a) CD4+ T cells from peripheral blood of a melanoma patient recognize peptides derived from nonmutated tyrosinase. Cancer Res 58: 296
70. Kobayashi H, Kokubo T, Takahashi M, Sato K, Miyokawa N, Kimura S, Kinouchi R, Katagiri M (1998b) Tyrosinase epitope recognized by an HLA-DR-restricted T-cell line from a Vogt-Koyanagi-Harada disease patient. Immunogenetics 47: 398
71. Kono K, Rongcun Y, Charo J, Ichihara F, Celis E, Sette A, Appella E, Sekikawa T, Matsumoto Y, Kiessling R (1998) Identification of HER2/neu-derived peptide epitopes recognized by gastric cancer-specific cytotoxic T lymphocytes. Int J Cancer 78: 202
72. Lethe B, Lucas S, Michaux L, De Smet C, Godelaine D, Serrano A, De Plaen E, Boon T (1998) LAGE-1, a new gene with tumor specificity. Int J Cancer 76: 903
73. Li K, Adibzadeh M, Halder T, Kalbacher H, Heinzel S, Muller C, Zeuthen J, Pawelec G (1998) Tumour-specific MHC-class-II-restricted responses after in vitro sensitization to synthetic peptides corresponding to gp100 and Annexin II eluted from melanoma cells. Cancer Immunol Immunother 47: 32
74. Lucas S, Brasseur F, Boon T (1999) A new MAGE gene with ubiquitous expression does not code for known MAGE antigens recognized by T cells. Cancer Res 59: 4100
75. Lucas S, De Plaen E, Boon T (2000) MAGE-B5, MAGE-B6, MAGE-C2, and MAGE-C3: four new members of the MAGE family with tumor-specific expression. Int J Cancer 87: 55
76. Lupetti R, Pisarra P, Verrecchia A, Farina C, Nicolini G, Anichini A, Bordignon C, Sensi M, Parmiani G, Traversari C (1998) Translation of a retained intron in tyrosinase-related protein (TRP) 2 mRNA generates a new cytotoxic T lymphocyte (CTL)-defined and shared human melanoma antigen not expressed in normal cells of the melanocytic lineage. J Exp Med 188: 1005
77. Lurquin C, De Smet C, Brasseur F, Muscatelli F, Martelange V, De Plaen E, Brasseur R, Monaco AP, Boon T (1997) Two members of the human MAGEB gene family located in Xp21.3 are expressed in tumors of various histological origins. Genomics 46: 397
78. Mandruzzato S, Brasseur F, Andry G, Boon T, van der Bruggen P (1997) A CASP-8 mutation recognized by cytolytic T lymphocytes on a human head and neck carcinoma. J Exp Med 186: 785
79. Manici S, Sturniolo T, Imro MA, Hammer J, Sinigaglia F, Noppen C, Spagnoli G, Mazzi B, Bellone M, Dellabona P, Protti MP (1999) Melanoma cells present a MAGE-3 epitope to CD4(+) cytotoxic T cells in association with histocompatibility leukocyte antigen DR11. J Exp Med 189: 871
80. Martelange V, De Smet C, De Plaen E, Lurquin C, Boon T (2000) Identification on a human sarcoma of two new genes with tumor-specific expression. Cancer Res 60: 3848
81. Minev B, Hipp J, Firat H, Schmidt JD, Langlade-Demoyen P, Zanetti M (2000) Cytotoxic T cell immunity against telomerase reverse transcriptase in humans. Proc Natl Acad Sci USA 97: 4796
82. Moreau-Aubry A, Le Guiner S, Labarriere N, Gesnel MC, Jotereau F, Breathnach R (2000) A processed pseudogene codes for a new antigen recognized by a CD8(+) T cell clone on melanoma. J Exp Med 191: 1617
83. Morel S, Levy F, Burlet-Schiltz O, Brasseur F, Probst-Kepper M, Peitrequin AL, Monsarrat B, Van Velthoven R, Cerottini JC, Boon T, Gairin JE, Van den Eynde BJ (2000) Processing of some antigens by the standard proteasome but not by the immunoproteasome results in poor presentation by dendritic cells. Immunity 12: 107
84. Morioka N, Kikumoto Y, Hoon DS, Morton DL, Irie RF (1995) Cytotoxic T cell recognition of a human melanoma derived peptide with a carboxyl-terminal alanine-proline sequence. Mol Immunol 32: 573
85. Nakao M, Shichijo S, Imaizumi T, Inoue Y, Matsunaga K, Yamada A, Kikuchi M, Tsuda N, Ohta K, Takamori S, Yamana H, Fujita H, Itoh K (2000) Identification of a gene coding for a new squamous cell carcinoma antigen recognized by the CTL. J Immunol 164: 2565
86. Noppen C, Levy F, Burri L, Zajac P, Remmel E, Schaefer C, Luscher U, Heberer M, Spagnoli GC (2000) Naturally processed and concealed HLA-A2.1-restricted epitopes from tumor-associated antigen tyrosinase-related protein-2. Int J Cancer 87: 241
87. Norbury LC, Clark RE, Christmas SE (2000) b3a2 BCR-ABL fusion peptides as targets for cytotoxic T cells in chronic myeloid leukaemia. Br J Haematol 109: 616
88. Ohminami H, Yasukawa M, Kaneko S, Yakushijin Y, Abe Y, Kasahara Y, Ishida Y, Fujita S (1999) Fas-independent and nonapoptotic cytotoxicity mediated by a human CD4(+) T-cell clone directed against an acute myelogenous leukemia-associated DEK-CAN fusion peptide. Blood 93: 925
89. Oiso M, Eura M, Katsura F, Takiguchi M, Sobao Y, Masuyama K, Nakashima M, Itoh K, Ishikawa T (1999) A newly identified MAGE-3-derived epitope recognized by HLA-A24-restricted cytotoxic T lymphocytes. Int J Cancer 81: 387
90. Oka Y, Elisseeva OA, Tsuboi A, Ogawa H, Tamaki H, Li H, Oji Y, Kim EH, Soma T, Asada M, Ueda K, Maruya E, Saji H, Kishimoto T, Udaka K, Sugiyama H (2000) Human cytotoxic T-lymphocyte responses specific for peptides of the wild-type Wilms' tumor gene (WT1) product. Immunogenetics 51: 99
91. Panelli MC, Bettinotti MP, Lally K, Ohnmacht GA, Li Y, Robbins P, Riker A, Rosenberg SA, Marincola FM (2000) A tumor-infiltrating lymphocyte from a melanoma metastasis with decreased expression of melanoma differentiation antigens recognizes MAGE-12. J Immunol 164: 4382
92. Parkhurst MR, Fitzgerald EB, Southwood S, Sette A, Rosenberg SA, Kawakami Y (1998) Identification of a shared HLA-A*0201-restricted T-cell epitope from the melanoma antigen tyrosinase-related protein 2 (TRP2). Cancer Res 58: 4895
93. Pawelec G, Max H, Halder T, Bruserud O, Merl A, da Silva P, Kalbacher H (1996) BCR/ABL leukemia oncogene fusion

peptides selectively bind to certain HLA-DR alleles and can be recognized by T cells found at low frequency in the repertoire of normal donors. Blood 88: 2118

94. Peiper M, Goedegebuure PS, Linehan DC, Ganguly E, Douville CC, Eberlein TJ (1997) The HER2/neu-derived peptide p654–662 is a tumor-associated antigen in human pancreatic cancer recognized by cytotoxic T lymphocytes. Eur J Immunol 27: 1115
95. Peoples GE, Goedegebuure PS, Smith R, Linehan DC, Yoshino I, Eberlein TJ (1995) Breast and ovarian cancer-specific cytotoxic T lymphocytes recognize the same HER2/neu-derived peptide. Proc Natl Acad Sci USA 92: 432
96. Pieper R, Christian RE, Gonzales MI, Nishimura MI, Gupta G, Settlage RE, Shabanowitz J, Rosenberg SA, Hunt DF, Topalian SL (1999) Biochemical identification of a mutated human melanoma antigen recognized by CD4(+) T cells. J Exp Med 189: 757
97. Robbins PF, el-Gamil M, Li YF, Topalian SL, Rivoltini L, Sakaguchi K, Appella E, Kawakami Y, Rosenberg SA (1995) Cloning of a new gene encoding an antigen recognized by melanoma-specific HLA-A24-restricted tumor-infiltrating lymphocytes. J Immunol 154: 5944
98. Robbins PF, El-Gamil M, Li YF, Kawakami Y, Loftus D, Appella E, Rosenberg SA (1996) A mutated beta-catenin gene encodes a melanoma-specific antigen recognized by tumor infiltrating lymphocytes. J Exp Med 183: 1185
99. Robbins PF, El-Gamil M, Li YF, Fitzgerald EB, Kawakami Y, Rosenberg SA (1997) The intronic region of an incompletely spliced gp100 gene transcript encodes an epitope recognized by melanoma-reactive tumor-infiltrating lymphocytes. J Immunol 159: 303
100. Robbins P (2000) Immune recognition of cancer – tumor antigens. In: Parmiani G, Lotze MT (eds) Tumor immunology: molecularly defined antigens and clinical applications. Harwood, London
101. Rongcun Y, Salazar-Onfray F, Charo J, Malmberg KJ, Evrin K, Maes H, Kono K, Hising C, Petersson M, Larsson O, Lan L, Appella E, Sette A, Celis E, Kiessling R (1999) Identification of new HER2/neu-derived peptide epitopes that can elicit specific CTL against autologous and allogeneic carcinomas and melanomas. J Immunol 163: 1037
102. Ronsin C, Chung-Scott V, Poullion I, Aknouche N, Gaudin C, Triebel F (1999) A non-AUG-defined alternative open reading frame of the intestinal carboxyl esterase mRNA generates an epitope recognized by renal cell carcinoma-reactive tumor-infiltrating lymphocytes in situ. J Immunol 163: 483
103. Russo V, Tanzarella S, Dalerba P, Rigatti D, Rovere P, Villa A, Bordignon C, Traversari C (2000) Dendritic cells acquire the MAGE-3 human tumor antigen from apoptotic cells and induce a class I-restricted T cell response. Proc Natl Acad Sci USA 97: 2185
104. Salazar-Onfray F, Nakazawa T, Chhajlani V, Petersson M, Karre K, Masucci G, Celis E, Sette A, Southwood S, Appella E, Kiessling R (1997) Synthetic peptides derived from the melanocyte-stimulating hormone receptor MC1R can stimulate HLA-A2-restricted cytotoxic T lymphocytes that recognize naturally processed peptides on human melanoma cells. Cancer Res 57: 4348
105. Scanlan MJ, Altorki NK, Gure AO, Williamson B, Jungbluth A, Chen YT, Old LJ (2000) Expression of cancer-testis antigens in lung cancer: definition of bromodomain testis-specific gene (BRDT) as a new CT gene, CT9. Cancer Lett 150: 155
106. Schneider J, Brichard V, Boon T, Meyer zum Buschenfelde KH, Wolfel T (1998) Overlapping peptides of melanocyte differentiation antigen Melan-A/MART-1 recognized by autologous cytolytic T lymphocytes in association with HLA-B45.1 and HLA-A2.1. Int J Cancer 75: 451
107. Shichijo S, Nakao M, Imai Y, Takasu H, Kawamoto M, Niiya F, Yang D, Toh Y, Yamana H, Itoh K (1998) A gene encoding antigenic peptides of human squamous cell carcinoma recognized by cytotoxic T lymphocytes. J Exp Med 187: 277
108. Skipper JC, Kittlesen DJ, Hendrickson RC, Deacon DD, Harthun NL, Wagner SN, Hunt DF, Engelhard VH, Slingluff CL Jr (1996) Shared epitopes for HLA-A3-restricted melanoma-reactive human CTL include a naturally processed epitope from Pmel-17/gp100. J Immunol 157: 5027
109. Suzuki K, Sahara H, Okada Y, Yasoshima T, Hirohashi Y, Nabeta Y, Hirai I, Torigoe T, Takahashi S, Matsuura A, Takahashi N, Sasaki A, Suzuki M, Hamuro J, Ikeda H, Wada Y, Hirata K, Kikuchi K, Sato N (1999) Identification of natural antigenic peptides of a human gastric signet ring cell carcinoma recognized by HLA-A31-restricted cytotoxic T lymphocytes. J Immunol 163: 2783
110. Tahara K, Takesako K, Sette A, Celis E, Kitano S, Akiyoshi T (1999) Identification of a MAGE-2-encoded human leukocyte antigen-A24-binding synthetic peptide that induces specific antitumor cytotoxic T lymphocytes. Clin Cancer Res 5: 2236
111. Tanaka F, Fujie T, Tahara K, Mori M, Takesako K, Sette A, Celis E, Akiyoshi T (1997) Induction of antitumor cytotoxic T lymphocytes with a MAGE-3-encoded synthetic peptide presented by human leukocytes antigen-A24. Cancer Res 57: 4465
112. Tanaka Y, Takahashi T, Nieda M, Masuda S, Kashiwase K, Ogawa S, Chiba S, Juji T, Hirai H (2000) Generation of HLA-DRB1*1501-restricted p190 minor bcr-abl (e1a2)-specific CD4+ T lymphocytes. Br J Haematol 109: 435
113. Tanzarella S, Russo V, Lionello I, Dalerba P, Rigatti D, Bordignon C, Traversari C (1999) Identification of a promiscuous T-cell epitope encoded by multiple members of the MAGE family. Cancer Res 59: 2668
114. ten Bosch GJ, Toornvliet AC, Friede T, Melief CJ, Leeksma OC (1995) Recognition of peptides corresponding to the joining region of p210BCR-ABL protein by human T cells. Leukemia 9: 1344
115. ten Bosch GJ, Joosten AM, Kessler JH, Melief CJ, Leeksma OC (1996) Recognition of BCR-ABL positive leukemic blasts by human CD4+ T cells elicited by primary in vitro immunization with a BCR-ABL breakpoint peptide. Blood 88: 3522
116. ten Bosch GJ, Kessler JH, Joosten AM, Bres-Vloemans AA, Geluk A, Godthelp BC, van Bergen J, Melief CJ, Leeksma OC (1999) A BCR-ABL oncoprotein p210b2a2 fusion region sequence is recognized by HLA-DR2a restricted cytotoxic T lymphocytes and presented by HLA-DR matched cells transfected with an Ii(b2a2) construct. Blood 94: 1038
117. Topalian SL, Rivoltini L, Mancini M, Markus NR, Robbins PF, Kawakami Y, Rosenberg SA (1994) Human CD4+ T cells specifically recognize a shared melanoma-associated antigen encoded by the tyrosinase gene. Proc Natl Acad Sci USA 91: 9461
118. Topalian SL, Gonzales MI, Parkhurst M, Li YF, Southwood S, Sette A, Rosenberg SA, Robbins PF (1996) Melanoma-specific CD4+ T cells recognize nonmutated HLA-DR-restricted tyrosinase epitopes. J Exp Med 183: 1965
119. Traversari C, van der Bruggen P, Luescher IF, Lurquin C, Chomez P, Van Pel A, De Plaen E, Amar-Costesec A, Boon T (1992) A nonapeptide encoded by human gene MAGE-1 is recognized on HLA-A1 by cytolytic T lymphocytes directed against tumor antigen MZ2-E. J Exp Med 176: 1453
120. Tsai V, Southwood S, Sidney J, Sakaguchi K, Kawakami Y, Appella E, Sette A, Celis E (1997) Identification of subdominant CTL epitopes of the GP100 melanoma-associated tumor antigen by primary in vitro immunization with peptide-pulsed dendritic cells. J Immunol 158: 1796
121. Tsang KY, Zaremba S, Nieroda CA, Zhu MZ, Hamilton JM, Schlom J (1995) Generation of human cytotoxic T cells specific for human carcinoembryonic antigen epitopes from patients immunized with recombinant vaccinia-CEA vaccine. J Natl Cancer Inst 87: 982
122. van Baren N, Chambost H, Ferrant A, Michaux L, Ikeda H, Millard I, Olive D, Boon T, Coulie PG (1998) PRAME, a gene encoding an antigen recognized on a human melanoma by

cytolytic T cells, is expressed in acute leukaemia cells. Br J Haematol 102: 1376

123. Van den Eynde B, Peeters O, De Backer O, Gaugler B, Lucas S, Boon T (1995) A new family of genes coding for an antigen recognized by autologous cytolytic T lymphocytes on a human melanoma. J Exp Med 182: 689
124. Van den Eynde BJ, Gaugler B, Probst-Kepper M, Michaux L, Devuyst O, Lorge F, Weynants P, Boon T (1999) A new antigen recognized by cytolytic T lymphocytes on a human kidney tumor results from reverse strand transcription. J Exp Med 190: 1793
125. van der Bruggen P, Traversari C, Chomez P, Lurquin C, De Plaen E, Van den Eynde B, Knuth A, Boon T (1991) A gene encoding an antigen recognized by cytolytic T lymphocytes on a human melanoma. Science 254: 1643
126. van der Bruggen P, Bastin J, Gajewski T, Coulie PG, Boel P, De Smet C, Traversari C, Townsend A, Boon T (1994a) A peptide encoded by human gene MAGE-3 and presented by HLA-A2 induces cytolytic T lymphocytes that recognize tumor cells expressing MAGE-3. Eur J Immunol 24: 3038
127. van der Bruggen P, Szikora JP, Boel P, Wildmann C, Somville M, Sensi M, Boon T (1994b) Autologous cytolytic T lymphocytes recognize a MAGE-1 nonapeptide on melanomas expressing HLA-Cw*1601. Eur J Immunol 24: 2134
128. Visseren MJ, van der Burg SH, van der Voort EI, Brandt RM, Schrier PI, van der Bruggen P, Boon T, Melief CJ, Kast WM (1997) Identification of HLA-A*0201-restricted CTL epitopes encoded by the tumor-specific MAGE-2 gene product. Int J Cancer 73: 125
129. Vissers JL, De Vries IJ, Schreurs MW, Engelen LP, Oosterwijk E, Figdor CG, Adema GJ (1999) The renal cell carcinoma-associated antigen G250 encodes a human leukocyte antigen (HLA)-A2.1-restricted epitope recognized by cytotoxic T lymphocytes. Cancer Res 59: 5554
130. Vonderheide RH, Hahn WC, Schultze JL, Nadler LM (1999) The telomerase catalytic subunit is a widely expressed tumor-associated antigen recognized by cytotoxic T lymphocytes. Immunity 10: 673
131. Wang RF, Appella E, Kawakami Y, Kang X, Rosenberg SA (1996a) Identification of TRP-2 as a human tumor antigen recognized by cytotoxic T lymphocytes. J Exp Med 184: 2207
132. Wang RF, Parkhurst MR, Kawakami Y, Robbins PF, Rosenberg SA (1996b) Utilization of an alternative open reading frame of a normal gene in generating a novel human cancer antigen. J Exp Med 183: 1131
133. Wang RF, Johnston SL, Southwood S, Sette A, Rosenberg SA (1998a) Recognition of an antigenic peptide derived from tyrosinase-related protein-2 by CTL in the context of HLA-A31 and -A33. J Immunol 160: 890
134. Wang RF, Johnston SL, Zeng G, Topalian SL, Schwartzentruber DJ, Rosenberg SA (1998b) A breast and melanoma-shared tumor antigen: T cell responses to antigenic peptides translated from different open reading frames. J Immunol 161: 3598
135. Wang RF, Wang X, Atwood AC, Topalian SL, Rosenberg SA (1999a) Cloning genes encoding MHC class II-restricted antigens: mutated CDC27 as a tumor antigen. Science 284: 1351
136. Wang RF, Wang X, Rosenberg SA (1999b) Identification of a novel major histocompatibility complex class II-restricted tumor antigen resulting from a chromosomal rearrangement recognized by CD4(+) T cells. J Exp Med 189: 1659
137. Wolfel T, Van Pel A, Brichard V, Schneider J, Seliger B, Meyer zum Buschenfelde KH, Boon T (1994) Two tyrosinase nonapeptides recognized on HLA-A2 melanomas by autologous cytolytic T lymphocytes. Eur J Immunol 24: 759
138. Wolfel T, Hauer M, Schneider J, Serrano M, Wolfel C, Klehmann-Hieb E, De Plaen E, Hankeln T, Meyer zum Buschenfelde KH, Beach D (1995) A p16INK4a-insensitive CDK4 mutant targeted by cytolytic T lymphocytes in a human melanoma. Science 269: 1281
139. Yang D, Nakao M, Shichijo S, Sasatomi T, Takasu H, Matsumoto H, Mori K, Hayashi A, Yamana H, Shirouzu K, Itoh K (1999) Identification of a gene coding for a protein possessing shared tumor epitopes capable of inducing HLA-A24-restricted cytotoxic T lymphocytes in cancer patients. Cancer Res 59: 4056
140. Yasukawa M, Ohminami H, Kaneko S, Yakushijin Y, Nishimura Y, Inokuchi K, Miyakuni T, Nakao S, Kishi K, Kubonishi I, Dan K, Fujita S (1998) CD4(+) cytotoxic T-cell clones specific for bcr-abl b3a2 fusion peptide augment colony formation by chronic myelogenous leukemia cells in a b3a2-specific and HLA-DR-restricted manner. Blood 92: 3355
141. Yotnda P, Firat H, Garcia-Pons F, Garcia Z, Gourru G, Vernant JP, Lemonnier FA, Leblond V, Langlade-Demoyen P (1998a) Cytotoxic T cell response against the chimeric p210 BCR-ABL protein in patients with chronic myelogenous leukemia. J Clin Invest 101: 2290
142. Yotnda P, Garcia F, Peuchmaur M, Grandchamp B, Duval M, Lemonnier F, Vilmer E, Langlade-Demoyen P (1998b) Cytotoxic T cell response against the chimeric ETV6-AML1 protein in childhood acute lymphoblastic leukemia. J Clin Invest 102: 455
143. Yun C, Senju S, Fujita H, Tsuji Y, Irie A, Matsushita S, Nishimura Y (1999) Augmentation of immune response by altered peptide ligands of the antigenic peptide in a human CD4+ T-cell clone reacting to TEL/AML1 fusion protein. Tissue Antigens 54: 153
144. Zarour HM, Kirkwood JM, Kierstead LS, Herr W, Brusic V, Slingluff CL Jr, Sidney J, Sette A, Storkus WJ (2000) Melan-A/MART-1(51–73) represents an immunogenic HLA-DR4-restricted epitope recognized by melanoma-reactive CD4(+) T cells. Proc Natl Acad Sci USA 97: 400
145. Zeng G, Touloukian CE, Wang X, Restifo NP, Rosenberg SA, Wang RF (2000) Identification of CD4+ T cell epitopes from NY-ESO-1 presented by HLA-DR molecules. J Immunol 165: 1153
146. Zorn E, Hercend T (1999a) A natural cytotoxic T cell response in a spontaneously regressing human melanoma targets a neoantigen resulting from a somatic point mutation. Eur J Immunol 29: 592
147. Zorn E, Hercend T (1999b) A MAGE-6-encoded peptide is recognized by expanded lymphocytes infiltrating a spontaneously regressing human primary melanoma lesion. Eur J Immunol 29: 602